Reiser: Ger. Oph. Soc. Trans. Heidelberg, July 6–8, 1936.
Rollet & Colrat: Arch. d'opht. **43**: 577, 1926.
Rosenow & Oftedal: J. Infec. Dis. **18**: 477, 1916; J.A.M.A. **64**: 1968, 1915.
Rossander: Hygiea, Stockholm, **39**: 7, 1877.
Sattler: Wien. med. Wchnschr. **9**: 327, 1889; Wien. med. Presse, p. 1044, 1875; Vrtljschr. f. Dermat. u. Syph., 1875; Wien. Protokol der Sitzung, Oct. 28, 1876.
Scheer, von der: Ztschr. f. d. ges. Neurol. u. Psychiat. **16**: 343, 1913; **34**: 119, 1913.
Strzeminski: Rec. d'opht. Paris, **20**: 19, 1898.
Sulzer, G. A.: Ophthalmology, **3**: 47, 1906.
Sunde: Norsk. mag. f. laegevidensk. **11**: 339, 1913.
Tacke: Ann. de l'Inst. chir. de Brux. **10**: 129, 1903.
Talkovskiy: Vestnik. oftal. 13–636. 1938.
Teague & Goodpasture: J.A.M.A. **82**: 1049, 1924.
Terrien: Arch. d'opht. **20**: 449, 1900.
Turner: In Wadsworth, Boston M. & S. J. **92**: 224, 1875.
Vendel: Ugesk. f. laeger, **85**: 222, 1923.
Wadsworth: Boston M. & S. J. **92**: 224, 1875.
Wagner: Arch. f. Heilk. **21**: 321, 1870.
Weidner: Berl. klin. Wchnschr. **7**: 321, 1870.
Wilbrand & Saenger: Die Neurologie des Auges, **2**: 1901.
Wohlwill: Ztschr. f. d. ges. Neurol. u. Psychiat. **89**: 171, 1924.
Wood: In Veasey, Trans. Am. Ophth. Soc. 1919.
Wyss: Arch. f. Heilk. **12**: 261, 1871.

THE OCULAR PATHOLOGY OF METHYL ALCOHOL POISONING*

WALTER H. FINK, M.D.
Minneapolis, Minn.

INTRODUCTION

Methyl alcohol poisoning in relation to the eye is of interest not only because it is clinically important, but also because the resulting pathologic processes in the eye are not fully understood.

Any one who studies the literature on the subject is impressed with the lack of uniformity of opinion as to the effects of methyl alcohol upon the ocular structures, and opinions concerning the toxicologic process are also at variance. Most of these are based upon conclusions drawn from clinical observation, autopsy reports, and the results of experimental work in animals.

* Condensed version made by the author from the candidate's thesis for membership accepted by the Committee on Theses.

The literature is practically devoid of reports of studies made upon pathologic specimens from the human eye. In most instances these reports were incomplete and the material was not fixed immediately, thus allowing postmortem degenerations to ensue. It is well known that the retina, even though it is refrigerated, will disintegrate at once, giving rise to an appearance that may be interpreted as a pathologic change resulting from the use of methyl alcohol. Another criticism of the early postmortem findings is that the fixing and staining process used was not adequate to reveal minute changes accurately. It seems, therefore, that whatever evidence we have as the result of human autopsy should be held in question.

Considering the ocular findings as the result of animal experimentations, doubt again arises. The fact impresses us that many of the conclusions reached concerning the effect of methyl alcohol on the human being are based upon the results of experimental work on animals by H. Holden[12] in 1890 and Birch-Hirschfeld[1] in 1900. We must be skeptical of such conclusions because Holden's work cannot be regarded as scientifically accurate. Likewise, Birch-Hirschfeld's work in 1900 should not be considered too seriously since he must have had some grave doubts as to its accuracy, for he repeated it in 1920.[2] Doubt as to the accuracy of the positive findings in Holden's and Birch-Hirschfeld's animal experiments is also strengthened by the critical work of de Schweinitz,[4] who was unable to produce results similar to theirs. Jonas Friedenwald[5] likewise obtained negative results and, like de Schweinitz, concluded that the results of the earlier work were probably erroneous. That this is possible is evident when we consider how rapidly postmortem changes in the retina occur. We must also consider artifact and defective staining technique. It is quite possible that the negative findings of de Schweinitz and Friedenwald are correct, and that animal experimentation is of no value in solving the problem. We are aware of the fact that animal

tissues do not always exhibit the toxic effects of drugs as do the tissues of the human.

The pathologic effect of methyl alcohol on the human is wide-spread and not confined to a specific action on the retina, as some authors would have us believe. It should, therefore, be considered not only as regards its effect upon the eye, but also as it affects the whole body.

Because of the uncertainty concerning these questions, further study of the subject is indicated. The following investigation was undertaken to obtain more concrete information and thus establish a more definite conception of the ocular pathology which is present in these cases.

TOXICITY OF METHYL ALCOHOL

The causes that give rise to the peculiarities of methyl alcohol poisoning have not been satisfactorily explained. There is a paucity of facts regarding the actual behavior of methyl alcohol in the animal organism, so that the underlying causes of its extreme toxicity are not clearly understood. There are, however, certain facts determined by animal experimentation and clinical observation which aid us materially in arriving at conclusions.

As a basis for formulating an opinion as to the toxicologic processes there are the following facts:

The lethal action of methyl alcohol may be effected through three different avenues of entrance into the system: ingestion, inhalation, and cutaneous absorption.

The presence of various impurities in the alcohol does not influence the toxic action, and it is generally believed that the effect is due to a property inherent in the methyl alcohol itself.

Methyl alcohol is a poison in which idiosyncrasy plays an important part—some persons are seriously affected by doses that would not harm others. In those in whom small doses cause serious toxic effects, there is an idiosyncrasy against this agent.

There is no evidence to show that a tolerance to methyl alcohol can be developed.

Man appears to be relatively more susceptible to a poison like methyl alcohol than is the dog or the rabbit, because it seems that poisons which affect the highly differentiated nerve structures very powerfully are more dangerous in proportion to the development of the nervous system.

The fate of methyl alcohol in the human body is not definitely known. There is evidence to suggest that it is not the methyl alcohol itself that is responsible for these poisonous effects, but some of the chemical by-products of incomplete oxidation. It appears that formaldehyde and formic acid are the chief toxic agents, although others may be present. The toxic effect is believed to be due to these poisonous combinations circulating in the blood and coming in direct contact with the tissues.

It has been demonstrated that the difference in the character of intoxication between ethyl and methyl alcohol is due to the metabolism of these substances following their administration. Whereas ethyl alcohol is oxidized into easily excreted products—carbon dioxide and water—methyl alcohol is only partially oxidized, and the products of this incomplete oxidation are formaldehyde and formic acid. Some investigators explain this difference in the metabolism of the two alcohols by the difference in their rate of oxidation. Methyl alcohol in slow oxidation generates formic acid, whereas in rapid oxidation it forms carbon dioxide and water; hence, when it oxidizes rapidly it is comparatively harmless, whereas in slow oxidation, which usually occurs in certain persons, it is exceedingly toxic. The variation in effect on individuals may, therefore, be explained partly by the rate of oxidation which takes place in the individual.

If this transformation of methyl alcohol into formaldehyde and formic acid takes place, we have an example of a poisonous compound forming two intermediate compounds which are much more toxic than the original compound was. It has

been estimated that formaldehyde is about 30 times, and formic acid six times, more toxic than methyl alcohol.

In considering formaldehyde as the intermediate product of oxidation, we must concede that, from a chemical standpoint, its formation is possible, but on viewing our experimental evidence we find very little to substantiate this claim. Most of the evidence is against its presence in the tissues, and the only positive evidence was found by Pohl,[20] who failed to find support for the view that any "considerable quantities" of formaldehyde are formed, but "it may be that formaldehyde is formed and that it is quickly converted into formic acid."

We must, therefore, conclude that if formaldehyde is present, it is present for but a short time, but sufficiently long to produce a toxic action.

We unquestionably have definite evidence that formic acid is present in the body. We know that it is excreted in the urine, but when it is formed, and how much is formed, are unknown. It is apparently the final oxidation product in many cases, although some individuals may have the power to decompose the methyl alcohol further into carbon dioxide and water. That formic acid is not present in the tissues to any great degree is evident if we depend upon the tissue analysis as a criterion. Pohl considered it probable that all the methyl alcohol administered is converted into formic acid and that part of the latter is then oxidized to carbon dioxide. As he did not find it in the tissues in any amount, Pohl concluded that either methyl alcohol itself or some one of its derivatives is retained in the body and is then slowly converted into formic acid. Bongers,[3] on the other hand, asserts that after the administration of methyl alcohol considerable quantities of it are excreted in the urine. It would seem from this that not all the methyl alcohol is converted into formic acid.

Various tests made upon the distillates from tissues appear to have established the fact that methyl alcohol, and not

formaldehyde or formic acid, is the principal recoverable toxic substance. It is only very rarely that even traces of formaldehyde and formic acid have been detected. It seems evident, therefore, that methyl alcohol itself is retained in the body for some time, and is apparently excreted unaltered or as formic acid, which evidently is slowly formed.

It seems that in many instances the human body has great difficulty in oxidizing methyl alcohol. It has been stated that but 3 per cent. of the body metabolism can be attributed to the methyl alcohol, which seems to be conclusive evidence of the inability of the body to cope with it.

It is believed by some observers that we are dealing with a more profound disturbance of the metabolism than is indicated by the simple failure of the body properly to oxidize methyl alcohol. Observations support the view that acidosis plays an etiologic rôle in the production of the symptoms following methyl alcohol poisoning. As in a number of other pathologic conditions in which there is a reduction of the reserve alkali of the blood, the exact significance of this reduction is not clearly understood. There is strong evidence suggesting that the disturbance of the acid-base balance may, in itself, cause definite anatomic changes. It must be conceded that acidosis might be an important factor in producing the poisonous action of methyl alcohol. Harrop and Benedict[9] were the first to treat a patient on this assumption. In the case reported by these authors there was a definite reduction in the reserve alkali and also the characteristic air hunger.

A highly significant feature of this phase of the problem is the slow elimination of the methyl alcohol or its conversion products from the organism, leading to a subtle danger in the form of accumulated toxic products. Investigators have indicated that the probable explanation of the poisonous character of methyl alcohol is not only the failure of combustion, but also the delay in elimination. According to Henderson and Haggard,[10] more than a week is required in eliminating the methyl alcohol acquired by a single large absorption. If

the exposure is repeated before the elimination is completed, a cumulative effect results; the amount absorbed at each exposure is added to that which remains uneliminated. A toxic concentration is thus gradually built up in the blood as a result of repeated exposure to concentrations that do not cause an appreciable effect on a single exposure. Placet[19] has shown that the complete elimination of wood alcohol requires five times as long as ethyl alcohol.

It appears evident, therefore, that the toxicity of methyl alcohol may to some degree be attributed to the fact that it remains for a long period in the animal organism, where it has time to produce varied and grave changes of a chemical and chemicophysical nature.

Most evidence points to the fact that the methyl alcohol is distributed very rapidly to all tissues and fluids of the body. There is practically no lag in the methanol-water concentration of the blood behind that found in any tissue at a particular instant, regardless of whether the animal was accumulating methanol, was in a steady state, or was eliminating methanol following exposure. Consequently, all kinds of tissue or body cells are exposed to practically the same methanol-water concentration, there being no selective accumulation, retention, or predilection. The results also show that the amount of methyl alcohol in the body or in a particular tissue can be estimated from a determination of the methyl alcohol in any tissue or fluid.

It seems, therefore, that, once consumed or inhaled, methyl alcohol quickly disperses to all tissues of the body, having no selective affinity, but apparently injuring, by direct action, the more highly specialized tissues of the retina, brain, kidneys, and liver, and to a lesser extent the other tissues. Experimental data confirm this fact as regards the eye, because it has been demonstrated that the substances produced in the body by poisoning with methyl alcohol readily penetrate the eye.

On the other hand, there is some evidence to prove that

methyl alcohol has a marked selective affinity for the most
highly differentiated nerve elements of man. According to
this evidence, the various organs do not show identical find-
ings in the fixation of methyl alcohol; the brain and other
nerve tissue exhibit a decided selectivity for this substance,
and contain the largest quantities. Liver, kidney, and
muscles then show decreasing proportions of methyl alcohol.
The specific affinity is in accord with what might be expected
from its lipoid make-up. This is explained by the fact that
the alcohols, like ether, chloroform, and other volatile nar-
cotics, are quite soluble in lipoids such as those characterizing
the nervous system. With equal concentration of ethyl and
methyl alcohol, methyl alcohol has the greater effect of modi-
fying the lipoid content of organs. It should also be noted in
this connection that there is a considerable increase in the
fatty acid and cholesterol content of the blood serum result-
ing from acute experimental poisoning with methyl alcohol.

Furthermore, experimental evidence indicates that there
is a greater absorption of methyl than of ethyl alcohol in the
retina.

It is of importance to trace the ultimate fate of methyl
alcohol in the body. Whereas ethyl alcohol is eliminated
from the body chiefly through the lungs, and, to a far greater
extent, oxidation in the tissues, methyl alcohol is also elimi-
nated through the lungs, but only to a small extent is it oxi-
dized in the tissues. It is stated that only about 10 per cent.
of the total amount of ethyl alcohol which disappears from
the body is eliminated in the expired air. For methyl alcohol,
on the contrary, more than 70 per cent. of the amount dis-
appearing from the body appears in the expired air.

Voltz and Dietrich[28] found that, after administration of 2 c.c. of
methyl alcohol per kilogram of the body weight of a dog, 24.3
per cent. was excreted in forty-eight hours, of which 21.5 per cent.
was in the expired air and 2.18 per cent. in the urine. As 36.7
per cent. was found in the body, it follows that only 39 per cent.
was oxidized in the body. If the caloric value of the methyl alcohol

oxidized is calculated, it will be found that this represents only about 3 per cent. of the total metabolism of the body. These results are in marked contrast to those obtained in ethyl alcohol under analogous conditions. It seems evident, therefore, that the bulk of poison is eliminated through the lungs, skin, and kidneys.

Comment.—It is difficult to draw conclusions from the data available. We must keep in mind that most of the positive evidence is the result of animal experimentation, and that it may not hold good for man. It is to be regretted that so little effort has been made to obtain toxicologic data from the bodies of persons dying of methyl-alcohol poisoning. In a few instances the tissues were analyzed for methyl alcohol only, but other studies have not been conclusive. Considering the number of fatalities from this cause, this does not speak well for the thoroughness of our scientific work. It is evident, therefore, that we are largely obliged to draw conclusions from suppositions that are based mainly on theory and animal experimentation.

It seems evident that methyl alcohol cannot be oxidized readily by some individuals and that it acts as a poison. It is likely that the toxic substances remain in the system as such, and are distributed to all the tissues. Because of the prolonged contact with the tissues, these substances cause pathologic changes, but more so in the highly specialized tissues, such as the central nervous system, the kidney, liver, etc. It is possible that the more highly developed tissues of the central nervous system are affected most because of their chemical structure and the resulting disturbance in their nutrition.

It does not seem logical, with the evidence at hand, to conclude that one specific substance causes the change. Instead, it would appear to be several factors. A profound change in the chemistry of the body, caused by a lack of chemical balance, such as is seen in acidosis, could be a factor. In addition to this, there could be a direct chemical

action of methyl alcohol itself, or combined with the products of oxidation.

The degree of these reactions naturally would vary with the individual tolerance or with the ability to cope with the drug.

It is significant that most of these cases do not experience an immediate toxic effect. It seems logical that if methyl alcohol were the only toxic agent, the profound toxic effect would be evident immediately upon taking the alcohol, because we know that it is absorbed and circulates in the blood, coming in contact with sensitive tissues almost at once. Instead, in most cases toxic symptoms do not appear until many hours later. This would point to the fact that the pathologic changes occur after some drastic chemical upheaval has taken place in the chemistry of the body, such as is seen in acidosis or as the result of oxidation.

Just what action is responsible for the pathologic change it is difficult to determine. We know positively that methyl alcohol is found in the tissues, but there is no definite evidence to prove the presence of formaldehyde or of formic acid in the tissues. We do know that formic acid is formed in the body, because it is excreted by the kidneys. The fact that it is excreted for so long a period suggests that the transformation into formic acid is a very gradual process. It may be immaterial as to the exact length of time the formic acid remains in the body, because a chemical of this degree of toxicity needs but a moment to produce pathologic changes.

In addition to methyl alcohol, its by-products are also toxic elements which, either alone or in combination with the alcohol, cause a profound alteration in the chemistry of the body cells. This change in the body chemistry could produce an acidosis which, in combination with the other factors, would cause pathologic manifestations in all tissues, especially in the tissues of lipoidal structure, such as the retina and brain. We know that these highly specialized tissues are always more sensitive and will show degenerative changes

even in a temporary upset which interferes with the normal metabolism of its cells.

From the data available it may be stated that some chemical combinations are not tolerated by the body so readily as are others. Perhaps one of those less tolerated by a large percentage of persons is methyl alcohol. Although some individuals have the metabolic ability to cope with this drug, most do not, and when methyl alcohol is taken into the body the abnormal metabolic processes that do occur produce chemical compounds that tend to act as poisons and alter the normal chemical balance which is so necessary for our well-being. It is generally known, and has been confirmed by the author's experiments on animals, that one of the oxidation products, namely, formic acid, can cause changes similar to those produced by methyl alcohol alone. It would not be correct to infer, because of the presence of formic acid in the body during the toxic process, that it alone is the important factor. It would be more correct to state that formic acid is one factor, and that it very likely acts in conjunction with methyl alcohol and other oxidation products to produce the pathologic changes. There is no conclusive proof that methyl alcohol alone is responsible for the poisonous effects, and until further evidence is available, the foregoing statement may stand as a possible deduction.

SUBJECTIVE OCULAR SYMPTOMS

VISUAL ACUITY DATA.—The visual acuity changes found in methyl-alcohol poisoning are fairly distinctive.

In the acute cases, the changes are sufficiently constant to be of diagnostic value. The characteristic visual change is, first of all, a sudden lessening of vision which may be of marked degree. This is followed in a few weeks by a slow improvement, but later by a gradual loss of vision which may progress to total blindness.

Comment.—It may be assumed that the initial loss of vision may be caused by the action of the chemical on the ganglion

cells, the nerve-fibers, or on both. Its sudden onset, followed in a few weeks by a return of vision, suggests that at first there is an edema of the tissues. The tissue cells are not necessarily all involved. Microscopic study shows that the cells may be destroyed in patches, with some fairly normal cells between the destroyed areas. It is conceivable that the edema which undoubtedly results will temporarily inhibit the action of these undestroyed nerve cells, causing a temporary total or almost total loss of vision. The edema may be localized in the nerve, the retina, or in both, but, judging from the ophthalmoscopic pictures, it occurs most frequently in the region of the papilla. When the ophthalmoscope does not disclose changes indicating the presence of edema, it may be that the edema is retrobulbar. It is also possible for retinal and choroidal edema to be present and not be visible with the ophthalmoscope.

After a few weeks the edema subsides, the ganglion cells which were not previously destroyed resume their function, and vision returns to a degree. Because of the disturbed nutrition resulting from the toxic effect on the cell and the edema during the acute process, many of these partially affected cells may die, thus accounting for the gradual second reduction in vision. The final visual acuity depends upon the number of cells that survive. In the last stage, only a few cells may remain sufficiently normal to function and the vision may practically be gone. In other cases where there is but a slight permanent loss of vision, only a few cells are destroyed.

In order to appreciate the statements just made a microscopic slide should be studied. In the retina we can see a total destruction of ganglion cells and, adjacent to these, cells may be seen ranging from normal to complete destruction. The edema is also definitely present, and must inhibit the metabolism of the still undestroyed cells.

In the chronic cases the gradual loss of vision follows the same process to a lesser degree. There is no sudden death of

the ganglion cells and very little edema is present, but, instead, there is a gradual loss of vitality due to the altered metabolism of these highly sensitized cells.

PERIMETRY DATA.—The perimetry findings are not characteristic. Scotomas are the most frequent finding, and may be single or multiple. A central scotoma is the one most constantly seen. There is often a peripheral contraction of the field, which varies greatly in degree and position.

Comment.—From what has been stated, it is evident that the toxic effect of methyl alcohol is diffuse and variable. The constant occurrence of scotomas suggests that the effect varies in intensity, some areas being profoundly affected. The frequency of the central scotoma would suggest that the papillomacular bundle is an important point of involvement.

Because the ophthalmoscopic picture so frequently indicates a retrobulbar involvement or an involvement of the optic disc with little or no visible change in the retina, it would seem logical to conclude that the scotomas are the result of edema of the optic nerve. We cannot be certain, however, that these scotomas are not the result of localized involvement of the retina also. The variability of the perimetry findings over a period of time is in keeping with the visual acuity, and can be explained on the same basis as was described under the head of Visual Acuity Data.

It seems evident that in the perimetry findings we cannot establish a rule as to the exact structure affected. Undoubtedly, both the retina and the nerve are involved in all cases, but in some, one or the other structure may show the predominating change. From the perimetric evidence alone one is inclined to consider the optic nerve as the portion chiefly involved because the perimetry findings are more characteristic of this type of change.

OBJECTIVE OCULAR FINDINGS

EXTERNAL DATA.—The objective findings give evidence of a disturbance in the pupillary and accommodation reflex arcs.

That the involvement varies is shown by the variable pupillary and accommodative reactions.

Ocular tenderness, both on pressure and on movement of the globe, is evidence of an ocular or retrobulbar congestion or edema. The picture can be described as phenomena that accompany an acute edema.

Comment.—As to the localizing value, the objective findings suggest an involvement of the entire nerve and vascular elements of the eyeball, with certain suggestions of retrobulbar involvement. There are also findings which prove that the reflex arcs of the pupil and accommodative mechanism are affected, which points to a central involvement. The presence of ptosis and the involvement of certain extra-ocular muscles suggest a diffuse involvement of nerves other than the optic, and pathologic changes may be located in the higher centers.

OPHTHALMOSCOPIC DATA.—From a study of the various ophthalmoscopic reports it is evident that the optic nerve is the structure most frequently involved during the acute stage.

The process may at first invade the retrobulbar portion of the optic nerve only, or it may spread forward to involve the papilla, or it may involve the papilla from the onset. Most reports make little or no mention of the retina except to refer to the retina surrounding the papilla.

There are indications of circulatory disturbance with edema. The picture varies from a congestion of the nerve head to an intense edema. Mention is made of the dilated retinal vessels.

The optic atrophy which follows is proportional in degree to the primary nerve involvement.

Comment.—It is evident from these data that the optic nerve is the portion of the visual apparatus primarily affected, and the process suggests an edema that may vary in degree. At least this would be one explanation for the ophthalmoscopic description given in the various cases re-

ported. In the greatest number of cases reported the optic papilla shows signs of congestion or edema of various stages. In these cases edema of the retina is present, but there is a gradual lessening in degree away from the disc. The retina not adjacent to the disc may show no signs of disease beyond a hyperemia.

It is difficult to understand this picture when the microscopic descriptions emphasize so strongly the retinal phase of the change and manifest so little evidence of optic nerve disturbance. It is, of course, possible that, by comparison, the retinal edema appears insignificant and gives the impression of a mere congestion, when in reality it is quite edematous. To put it another way, we might say that the marked optic nerve picture seen with the ophthalmoscope does not preclude the absence of edema or destruction of the retinal elements. The absence of definite choroidal changes would tend to minimize the retinal ophthalmoscopic picture.

An opinion may be ventured that in those cases in which the optic nerve change is the predominating factor, a similar involvement occurs in the retina and choroid, but this is not shown ophthalmoscopically except for what appears to be hyperemia. The direct action of the toxemia in the retina may cause necrosis, but with little reaction visible with the ophthalmoscope.

Undoubtedly, some cases are more definitely retrobulbar than others, whereas others show more intra-ocular changes. It seems that on examination all cases will exhibit some signs of involvement of both elements.

Another factor that indicates a more general involvement than merely that affecting the optic nerve is the postneuritic atrophy which develops. In these cases reports show the presence of retinal atrophy as well.

It seems plausible, therefore, to conclude that the ophthalmoscopic evidence bears out the contention that the entire nerve structure of the eye, including the retina and optic nerve, is involved. In addition to this there is a choroidal

disturbance. The process is not always the same; instead, one part may show the predominating picture of disease.

It seems evident that the initial tissue injury is manifested as an edema or hyperemia only with the ophthalmoscope, and, undoubtedly, many retinal changes which are not conspicuous with the ophthalmoscope, but are none the less important, may not be seen.

MICROSCOPIC EVIDENCE FOUND IN THE HUMAN EYE

The following is a summary of the significant findings in the reported cases:

In the autopsies reported by Pick and Bielschowsky,[18] the most interesting histologic findings appeared in the ganglion-cell layer of the retina. In comparison with the ganglion cells, the other layers of the retina were only slightly altered. In these layers tangible changes were demonstrable only in the inner granular layer, where an agglomeration of the chromatic substance into coarse masses had taken place.

In the retrobulbar section of the optic nerve changes were found which, however, in comparison with those in the retina, seemed trivial. In occasional medullary sheaths, a fine-grained fatty degeneration was found. At some points there were to be noted swellings and inflations in the axis-cylinders. If all these findings in the optic nerve are considered together, we may say with certainty that an acute destruction of the nerve substance must have taken place.

In the central nervous system there were both chronic and recent changes in all three cases. The chronic changes were, no doubt, due to chronic alcoholism in each case. The acute changes were exclusively in the ganglion cells. Compared with the changes in the retina, these were only trivial, both from a quantitative as well as a qualitative point of view.

Comment.—These findings are very significant, since they describe in considerable detail the results found in the retina, optic nerve, and the higher centers of three cases dying of acute methyl alcohol poisoning. It is the most complete description in the literature of this condition, and most important in drawing conclusions. There is, however, the ques-

tion of postmortem changes being present, and there is no way of determining this point. It may be stated that the changes described are suggestive of postmortem changes. This similarity is emphasized by a study of the author's cases in which postmortem changes occurred. The similarity is striking.

Pick and Bielschowsky's statement that the most important changes occurred in the ganglion cells bears out the findings obtained in animal experimentation. They also stress the fact that the changes in the optic nerves were slight in comparison. In spite of the fact that they minimize the optic nerve changes, there is evidence of pathologic changes which should not be minimized. The degenerative changes in the medullary sheaths and the swelling of the nerve-fibers are definite signs of optic nerve injury.

In the central nervous system the finding of ganglion-cell destruction is significant and shows that the process is not confined to the eye.

The case reported by Rymowitsch[22] was that of a man who died of chronic methyl alcohol poisoning. The investigator noted hydropic and fatty degeneration of the retinal ganglion cells, varicosé hypertrophy of the nerve-fibers, and edematous saturation of the granular layers. No detailed account was recorded.

Comment.—The report is too brief to be of scientific value. It does, however, indicate changes in the retina which seem to be characteristic.

In Schwartz's[24] two cases dying of methyl alcohol poisoning the following findings were noted: There were no changes in the optic nerves; there were alterations, however, in the vagus and phrenic nerves. Changes in the retina were found that accounted for the blindness.

Comment.—The report is too brief to be of scientific value. It is significant that no changes were found in the optic nerves. The changes in the retina, vagus, and phrenic nerves were, unfortunately, not described.

In MacDonald's[15] three cases that died as a result of imbibing methyl alcohol the following changes were found:

Case I.—The retina showed marked degeneration in the ganglion-cell layer. The vessels of the choroid were considerably congested.

Case II.—The ganglion cells were decreased in number and degenerated, and cystic spaces were seen throughout this layer. The vessels of the choroid were markedly congested.

Case III.—The retina showed marked changes. The ganglion cells were decreased in number, and cystic spaces were seen throughout this and the nerve-fiber layer.

In view of the well-known early postmortem degenerative changes that take place in the delicate ganglion-cell structure, MacDonald could not say that his findings were of value. They suggest that the central scotoma and loss of vision are due to toxic degenerative changes that take place in the ganglion cells. He believes that the changes that occur later and which result in optic atrophy are due to ascending degeneration of the nerve-fiber following the damage to the ganglion cell. The optic nerve changes he believes are apparently late, as no pathologic alteration could be observed in the optic nerves of any of his cases.

Comment.—Without doubt, postmortem changes are responsible for some of the tissue changes mentioned, and it is difficult to evaluate this author's findings. The cases were so acute that the pathologic changes had not progressed very far. It is important to note the absence of signs of edema in the retina, as well as the absence of pathologic signs in the optic nerves.

In Menne's[17] two cases dying of methyl alcohol poisoning the following points were noted:
Microscopically, little change in the optic nerves was seen beyond edema and hyperemia and some patchy proliferation of glial cells. The most pronounced alterations were observed in the ganglion cells of the retinas. These changes in the ganglion-cell layer were most marked nearest the disc. Except for marked edema, there were no noteworthy changes in the glial cells.

Comment.—It is important to note the presence of edema of the optic nerve and the fact that the ganglion layers again

showed the greater change. Edema of the retina was also observed. It is unfortunate that more details were not given so that a proper evaluation of the findings could be made.

AUTHOR'S CASES.—Two cases are reported that died of methyl alcohol poisoning. The interpretation of the findings was as follows:

CASE 1, No. 70959 A.—There appears to be a small amount of papilledema. There is disintegration of the elements in the rods and cones forming an albuminous-like precipitate. There is a wealth of ganglion cells, and this layer does not show any evidence of increased gliosis. However, practically all the ganglion-cell nuclei are pushed to the extreme periphery of the cell. In many of the cells the Nissl substance is arranged in a peripheral ring, whereas in other cells there is more advanced dissolution of the Nissl substance, indicating chromatolytic changes. There is definite swelling of all the ganglion cells, including those in the macular region. This is perhaps an early stage of a destructive process.

No. 70959 B.—This eye is similar to the preceding one.

CASE 2, No. 70958 A.—There is a definite edema of the nerve head that is more marked than in the preceding eye. There seems also to be an increase in the glial elements in the nerve-fiber layer of the retina surrounding the disc and going into the optic nerve. The rod and cone layer has undergone dissolution. The ganglion cells are quite plentiful, but there is an increased number of glia cells in this layer. The ganglion cells themselves are swollen. The nuclei tend to bulge peripherally from the cell body. The Nissl substance has disintegrated, and in some cells is placed peripherally; in others it has taken on a fine granular appearance, and in still others the cell has only a ghost appearance. It seems that many of the ganglion cells in the macular region are better preserved than are those in the periphery.

No. 70958 B.—This eye is similar to No. 70958 A. There is an occasional normal ganglion cell, however, and in places the retina is detached because of the great accumulation of débris from the disintegrated rod and cone layer.

The nerves of Nos. 70958 A and B appear normal. No. 70959 B nerve shows some pink-staining areas which have the characteristics of edema. The other nerve appears to be normal.

Comment.—In these cases there should have been obvious postmortem changes in the retina because the specimens were not fixed in formalin until twelve hours after death. However, the material was refrigerated. Evidently some of the changes are postmortem. It is significant that they correspond very closely to the reported retinal changes of the other cases, and the question naturally arises as to how many of these are due to postmortem changes.

In the author's cases the engorged choroidal vessels and the edema of the retina are worthy of note. Also of importance is the presence of optic nerve changes in one case.

To draw conclusions from the preceding autopsy reports is difficult. First, there were not a sufficient number of cases. Second, the reports are not complete. Third, there is a possibility that the tissues were not fixed immediately and that many of the findings are the result of postmortem changes.

The findings which are most significant emphasize the retinal changes, which are chiefly in the ganglion layer. We should bear in mind that postmortem processes would cause alterations similar to these. Undoubtedly, some of the changes are the result of the toxic process, but, to be scientifically accurate, it is difficult to be sure how many are actually due to this cause.

It is somewhat significant that there were few changes in the optic nerves. Although there were some alterations which suggested a toxic process, many were undoubtedly postmortem.

If we can assume that the reported findings are not postmortem, then indeed we have valuable data. In that case we can say with assurance that the retina, especially the ganglion cells, suffers most from the toxic exposure. This would be expected because of the greater sensitivity of the latter to change. The presence of injury to the ganglion cells in the brain is evidence that similar changes are to be found elsewhere in the body.

The presence of degenerative changes in the optic nerves

of some of the cases shows that the process is not confined to the retina alone. Likewise, the edema is present in both the retina and the optic nerve. The absence of pathologic changes in the optic nerve may, in many instances, be due to the acute process, the type of tissue arrangement in which early changes may not show so readily, and the possibility of improper staining to show these early changes.

The presence of choroidal congestion appears to indicate that the vascular portion of the eye is involved. Some observers claim that the entire process is a vascular one, but, judging from the foregoing description, this does not appear to be the case. We must admit that the evidence of changes in the human is the most tangible argument we can present as to the pathologic conditions resulting from methyl alcohol poisoning.

ANIMAL EXPERIMENTATION CARRIED OUT BY OTHERS TO DETERMINE THE EFFECT OF METHYL ALCOHOL ON THE OCULAR STRUCTURES

The essential facts concerning these experiments are as follows:

Holden[11] found in a dog degenerative changes in the ganglion-cell and the nerve-fiber layers of the retina, and the medullary sheaths of the fibers of the optic nerve. He concluded that the retina is affected primarily, and that the optic nerve change represents a secondary stage of the process.

Comment.—It is somewhat impractical to draw any conclusions after an investigation on one dog. Suspicion is aroused that postmortem changes may have given rise to errors in evaluating the findings.

Birch-Hirschfeld[1] experimented with rabbits and chickens and found the following: The poison effect first made itself felt in the ganglion cells of the retina. After this the inner granules, and later the outer granules, degenerated.

Only in one case could distinct signs of degeneration of the nerve-fibers be found, and that was in the animal that showed the greatest

changes in the retinal layers. This was in a temporal wedge-shaped region of the cross-section beginning immediately back of the bulbus. There was distinct disintegration of fibers, extending backward for about 5 mm., whereas the remainder of the cross-sections showed fairly normal conditions. In the stained preparations no sign was found of round-cell infiltration, even in the degenerated region, nor a noteworthy connective-tissue proliferation.

Birch-Hirschfeld stated further that, without doubt, the degenerative changes in the optic nerve were of a secondary nature. This is indicated by their absence in the other cases, where the poisonous effect on the retinal cells was less marked.

Comment.—This study is undoubtedly significant, and has been recognized as such in the literature, since it has been referréd to repeatedly. If we adopt a critical attitude, we will consider the fact that these findings apply to rabbits and chickens, and are not necessarily indicative of what may be found in the human. There is also the possibility of other factors entering into the situation that may produce some of the alterations. One of these factors may be the postmortem changes which appear so rapidly in the retina, and the other one could be trauma, the result of killing the animal. Imperfect staining and fixing must also be considered.

If this investigator's work is scientifically accurate, his data bear out his contention that methyl alcohol, even in small doses in the experimental animal (rabbit and chicken), in the first place appreciably injures the cells of the retina; and that only in secondary fashion can the degenerative processes in the optic nerve occur. There must have been some doubt in Birch-Hirschfeld's mind as to the accuracy of this work, because in 1920 he repeated his studies.

Friedenwald,[5] working on a rabbit, observed the toxic effect on the ganglion cells of the retina. The retinal ganglion cells showed marked degeneration, whereas the inner and outer nuclear layers were less affected.

Comment.—The same criticism may be applied to this work as was applied to Holden's. Insufficient data were presented to substantiate the conclusions.

Tyson and Schoenberg,[27] experimenting on guinea-pigs, rabbits, dogs, and a monkey, concluded that microscopic findings indicated that there was an edema of the tissues, with very early signs of beginning degeneration of the ganglion layer of the retina.

These observers found: Choroid gives the impression of hyperemia. Retina: rods and cones and the external nuclear layer, normal. Outer reticular layer, slightly edematous. Inner nuclear layer, normal. Inner reticular layer, slight edema. Ganglion cells swollen and surrounded by clear areas, the nuclei being displaced far toward the periphery. Inner layers of the retina show some edema. The medullary sheath of the optic nerve takes Weigert's stain rather weakly.

Comment.—This work is especially significant since it confirms the findings of retinal degeneration with ophthalmoscopic evidence to support it.

The change in H-ion concentration of the aqueous and evidence of acidosis are suggestive of chemical changes in the eyeball which substantiate to a measure the theory of these workers as to the process leading to retinal degeneration.

Their evidence of increased susceptibility of high animals is valuable; of special significance is their contention that methyl alcohol is a true hematoxic and produces a degenerative change in all tissues.

Kazas,[14] in his work on the effect of methyl alcohol on rabbits, found that the general picture of changes in the retina, with the exception of the degenerative process, presented the phenomena of dropsical saturation. The degeneration was not always connected with dropsy. Changes in the retina were markedly manifested in all its layers, including the layer of rods and cones. An adipose degeneration of high grade was found, not only in the layer of nerve-fibers, but also in the ganglion-cell layer, in the cells proper, and in the inner molecular and nuclear layers.

Adipose degeneration was present in all optic nerves. A considerable increase of connective tissue was found. There was adipose degeneration in marked degree in the oculomotor nerve and the chiasma.

Kazas therefore succeeded in obtaining changes as follows: in the vascular membrane; in the membranes of the optic nerve; in the retina, beginning with dropsy and degeneration and going on to

albuminuric retinitis; and in the optic nerve, beginning with parenchymatous degenerative neuritis up to axial atrophy.

Comment.—This investigator's work appears to confirm the previous studies on this subject. The microscopic picture reported is in agreement with the work of others, although Kazas lays special stress on the independence of the degenerative changes and the edema. The finding of adipose degeneration in the optic nerve and the oculomotor nerve is especially important. The increase of connective tissue is significant. His contention that the affection of the nerves was independent of the retinal changes is also to be considered. His explanation of the pathologic process is worthy of attention.

Igerscheimer and Verzar[13] endeavored to determine whether the sense of light might be used as a clinical criterion of the action of poison upon the retina; as experimental animals they chose chickens.

They concluded that light perception was temporarily impaired three weeks after the onset of the poisoning. There was then complete restoration of light perception. After four additional weeks of poisoning, the perception of light was again reduced. The retina showed no changes of note.

Comment.—The significance of this investigation is that no pathologic changes were found in the chickens' eyes. The technique of applying the drug was apparently correct, and the method of sectioning the eyes was apparently not at fault. These observers emphasize the fact that acute intoxication was avoided, and it is possible that this may account for the absence of retinal pathology. The fact remains that, under careful experimental conditions, the retina did not show evidence of disease.

Schanz[23] believed that, between the swallowing of the poison and the oncoming blindness, there is an interval in which the light has a sensitizing effect which must be necessary for the poison to be effective. As an experimental confirmation of this theory he gave methyl alcohol to three rabbits, protected one eye from light, and exposed the other to the sun for a number of hours, five or six times in the course of several weeks.

He regarded the intoxication amblyopia as a sensitization injury to the retina, which absorbed more light and, above all, short-wave light, under the influence of sensitizers. In one of the rabbits that received the methyl alcohol and was killed on the nineteenth day after the last exposure he found "rather large exudates in the lower half of the retina of the exposed eye, while the protected eye was free from every change."

Schanz found a distinct diffuse degeneration of the entire cross-section of the optic nerve back of the point where the vessels entered in the exposed methyl alcohol eye. The optic nerves of the eye kept in darkness were found to be normal.

Comment.—This experiment does not prove anything of value. The data are insufficient from which to draw conclusions. The theory that light, acting in conjunction with the methyl alcohol, is a factor in producing retinal changes is a new approach, but does not appear to have much basis for acceptance.

In 1920 Birch-Hirschfeld[1] repeated his experiments, using dogs and monkeys. He found distinct signs of degeneration (analogous to those previously found in rabbits and chickens after the same form of intoxication) present in the ganglion cells.

Extensive degenerative changes could be observed, even in the beginning portion of the medullary optic nerve, immediately behind the lamina cribrosa. These changes did not appear in the entire cross-section. There were all stages of change, ranging from beginning partial degeneration of individual fibers to practically complete disintegration of the entire bundle; but in the degenerated areas distinct changes were apparent.

The primary change of the glia tissue rests upon a degenerative process; this degenerative process Birch-Hirschfeld assumed to be due to edematous saturation, leading to loosening and disintegration of the fibers.

He concluded that the degeneration of the nerve-fibers in the optic nerve was not the result of pressure necrosis due to the proliferated septum tissue or similar tissue showing inflammatory infiltration.

In view of this, and of the normal macroscopic condition of the optic nerve with reference to the size of the cross-section and consistency, the author assumed that the exudative processes in the nerve-trunk had not yet fully developed.

Comment.—This work confirmed Birch-Hirschfeld's earlier findings, and, in addition, demonstrated their presence in higher forms of animals, such as the monkey. His conclusions concerning the optic nerve findings, especially the changes in the nerve-fibers, seem to be more definite in this work.

He stresses the absence of inflammatory reaction and edema, although the nerve tissue showed extensive degeneration in areas. The degeneration also involved the glia tissue, and this would suggest that it is the result of the direct action of the poison.

De Schweinitz[4] examined dogs acutely and chronically poisoned by methyl alcohol, and in no case did microscopic study reveal pathologic changes in the retina.

Comment.—These findings are of special significance. Although the work is brief, it is, as characterizes all this author's work, very reliable. The absence of positive findings is in wide variance with other similar work and leaves it all open to question.

Friedenwald and Felty[7] performed similar experiments, using rabbits, guinea-pigs, and dogs.

They were unable to produce any retinal or optic nerve lesions with methyl alcohol, and they concluded that the original reports of Birch-Hirschfeld in regard to alleged changes in ganglion cells were artefacts, since they could produce similar changes in material from normal animals by variations in fixation and embedding.

Comment.—It is of value to compare the methods used with those used by others who did find retinal changes. Friedenwald is an accurate observer, and this adds weight to the importance of his findings.

Schwarzkopf[25] experimented with rabbits and dogs, and studied the effect of light in relation to ocular changes.

Retina: Pronounced degeneration, chiefly in the ganglion cells. Inflation of the cell body and nucleus to the point of obliteration of the cell boundaries, alternate with shrinkage processes and clumping of the chromatin. No edema. Vessels normal. Inner granules: chromatin structure not distinct, inflation, and chromatolysis.

Optic nerve: Bilateral diffuse degeneration of the optic nerve immediately behind the bulbus, almost to the point of entrance of the vessels. Enlargement of the septa and multiplication of nuclei only in the anterior sections. No inflammatory infiltration.

Comment.—Schwarzkopf's anatomic investigations are a complete confirmation of the Birch-Hirschfeld results. In the retina, the ganglion-cell layer displayed the first and most conspicuous changes. It is especially significant that he found degenerative changes in the optic nerves immediately behind the eyeball.

Scott[26] performed experiments on 31 monkeys, 58 rabbits, and 176 white mice.

In studying the eyes and optic nerves, this writer found constant changes both in the retina and in the nerve. However, the changes in the retina predominated and were uniformly of the nature of an acute toxic lesion. The vessels of the choroid were markedly congested. The entire retina was edematous, but especially the fiber and ganglionic-cell layers. The ganglion cells were degenerated. This degeneration was patchy, normal areas being immediately adjacent to markedly degenerated areas. These degenerated regions were not confined to any one area of the retina, but were scattered throughout the structure. These retinal changes are quite similar to those found by MacDonald in human cases, and by Holden, Friedenwald, Tyson and Schoenberg, and Birch-Hirschfeld in experimental animals. It was not uncommon to find degenerations in the retina without any degenerative changes present in the optic nerve.

Comment.—As in other studies on animals, the retinal changes seem to predominate. The findings in these experiments were in accord with the changes found by other investigators.

In summarizing the results of this experimental work, it is interesting to note that nine papers reported finding definite pathologic changes in the retina and optic nerve. In three papers the writers failed to find evidence of change.

In all nine instances the findings were in fair agreement. In describing the retina, it was common to find that the

alterations consisted of definite degenerative changes in the ganglion cells and a change of lesser degree in the other layers.

As regards the optic nerve changes, all nine authors found evidence of pathologic changes, and it seemed common to find degenerations in the retina associated with the degenerative changes in the optic nerve. The retinal changes seemed to predominate.

It is especially significant that degenerative changes in the optic nerves were found immediately behind the eyeball. Most of the writers agreed that the degenerative changes in the optic nerve were less conspicuous. The following quotations are characteristic:

"In cross-sections, extensive degenerative changes could be observed even in the beginning portion of the medullary optic nerve, immediately behind the lamina cribrosa. These changes did not appear in the entire cross-section. There were all stages of change ranging from beginning partial degeneration of individual fibers to practically complete disintegration of the entire bundle, but in the degenerated areas there were distinct changes."

"In the preparations was found no sign of round-cell infiltration even in the degenerated region, or a noteworthy connective-tissue proliferation."

"The primary change of the glia tissue rests upon a degenerative process; this degenerative process, it was assumed, was due to edematous saturation which leads to loosening and disintegration of the fibers. The degeneration of the nerve-fibers in the optic nerve was not the result of pressure necrosis due to the proliferated septum tissue or similar tissue showing inflammatory infiltration."

It seems that the constant finding in both the retina and the optic nerve was edema. This was associated with signs of necrosis or degeneration of all parts, but especially of the higher differentiated cells of the retina. There was no evidence of inflammatory infiltration or vascular engorgement except for a slight amount in the choroid.

Contrary to the foregoing are the negative results found in the work of de Schweinitz and Friedenwald. It is difficult to

explain the difference in result. As the details of the experimental work of these observers were not published, it is impossible to make a fair analysis. It might be of value to mention that de Schweinitz must still have been in doubt, in spite of his experimental work, because he suggested that this problem should be solved. The findings of two such reliable observers should be considered significant. The following statement by Friedenwald should be borne in mind in making a final decision:

"The original findings of Birch-Hirschfeld in regard to alleged changes in the Nissl bodies of the ganglion cells were artefacts, since he could produce similar changes in material from normal animals by variations in fixation and embedding."

ANIMAL EXPERIMENTATION CARRIED ON BY THE AUTHOR TO DETERMINE THE EFFECT OF METHYL ALCOHOL ON THE OCULAR STRUCTURE OF ANIMALS

In drawing conclusions from the researches carried out by the author, certain definite statements may be made.

The experiments were performed as a check on the work of others. There was some doubt as to the accuracy of the previous technique used, and it was believed by some writers that the findings were artefacts due either to improper staining or to postmortem changes.

In this work certain technical errors have been eliminated. The chemicals were given as designated; the eyes were immediately fixed; the microscopic slides were made by experts, and were interpreted by a skilled eye pathologist who had no information as to what treatment the animal had received.

In addition to improving the technique, the problem offered an opportunity to decide the question of the importance of impurities in methyl alcohol. The question of formic acid was also considered.

Some workers hold the opinion that the toxic effect of methyl alcohol is due to the oxidation products. As we know that formic acid is actually produced in the system as the

result of oxidation, it was considered advisable to use this knowledge in certain cases for comparison of results.

Another phase of the problem that proved to be of value was the fact that a group of animals was carried over a period of two months in order to determine the effect of prolonged poisoning. Most of the previous work was done on cases of acute poisoning. It was hoped that this might yield further information as to the pathologic reaction.

Observation showed that there was an individual variation in the toxic reaction in the various animals, and possibly a greater toxic reaction in the dog. No difference could be determined in the reaction of the animals given pure methyl alcohol as compared with those that received commercial methyl alcohol.

The reaction to the methyl alcohol and the formic acid seemed practically the same, although in certain instances some of the animals reacted more violently to the formic acid.

At no time did the ophthalmoscope supply evidence of intra-ocular disturbance that would suggest edema. although it must be admitted that repeated examinations to eliminate this point absolutely were practically impossible and not made. No apparent visual disturbances were noted.

The following is a brief summary of the positive microscopic findings:

ACUTE POISONING

Rabbit 1.—Pure methyl alcohol given. A relatively early stage of acute intoxication, with early chromatolysis of the ganglion cells.

Rabbit 2.—Pure methyl alcohol given. Nerve head appears normal. Marked vacuolization of the cytoplasm of the large ganglion cells with practically complete disappearance of the Nissl substance. This is definitely more advanced chromatolysis than in rabbit 1.

Rabbit 3.—Commercial methyl alcohol given. There is practically complete dissolution of the rod and cone elements, with a thickening of the subretinal space because of apparent albuminous accumulation. Many of the ganglion cells have been reduced to shadow forms, whereas others of the large variety have advanced vacuoliza-

tion. Judging from the increased number of tissue spaces, there may be some edema of the ganglion-cell and nerve-fiber layers.

Rabbit 4.—The same drug given as in rabbit 3. The rods and cones are quite completely disorganized, and there are the usual thickening and albuminous appearance of the subretinal space. The ganglion cells show an advanced stage of chromatolysis. There may be a small amount of edema of this retina.

Rabbit 5.—Formic acid given. The picture is the same as in rabbit 4.

Dog G.—Pure methyl alcohol given. There is early disintegration in the ganglion cells, and an early acute stage of chromatolysis due to intoxication.

Dog H.—Pure methyl alcohol given. An edema of the nerve head is present. There are marked disintegration and infiltration of the rod and cone layer and the subretinal space. The number of ganglion cells is reduced, and those that are present show marked evidence of degeneration, especially of the cytoplasm.

Dog I.—Commercial methyl alcohol given. The nerve and nerve head are apparently normal. These cells are perhaps in an intermediate stage of chromatolysis.

Dog J.—Commercial methyl alcohol given. There is some edema of the disc of the nerve head. The ganglion cells seem to be reduced in number.

Dog K.—Formic acid given. There is an exudate on, and perhaps some edema of, the nerve head. The ganglion cells are undergoing acute chromatolysis with dissolution of the cells. Apparently acute chromatolysis by an overwhelming dose of poison.

Dog L.—Formic acid given. There is marked edema of the nerve head. A most profound reaction that may lead to a degeneration of the retina is perhaps early.

CHRONIC POISONING

Rabbit 6.—Pure methyl alcohol given. The rods and cones show a large amount of disintegration.

Rabbit 8.—Pure methyl alcohol given. There is moderately advanced disintegration of the rod and cone elements. Some of the ganglion cells have been reduced to shadow forms.

Rabbit 9.—Commercial methyl alcohol given. These ganglion cells are only slightly affected. Practically all the ganglion cells are involved in the process.

Rabbit 10.—Commercial methyl alcohol given. There is moderate disintegration of the rod and cone elements. The ganglion cells appear washed out and poorly stained, and much of the cytoplasm is homogeneous. The appearance of these ganglion cells is as if hit hard by a powerful blow.

Rabbit 12B.—Formic acid given. Rods and cones considerably disintegrated. The usual signs of chromatolysis are present, those indicating disintegration in general.

Rabbit 13B.—Formic acid given. Some disintegration of the rod and cone elements. The ganglion cells are not so abundant as in other specimens, and some show quite marked degeneration.

Dog A.—Pure methyl alcohol given. The optic nerve is essentially normal. The rod and cone layer of the retina is completely disorganized, and there seems to be an increased albuminous fluid content. This appears to be a degenerative process of the rod and cone nuclei rather than a postmortem autolytic phenomenon. The ganglion-cell layer seems to contain an increased number of glial cells and a diminished number of ganglion cells. Of the few ganglion cells that remain, many are in an advanced stage of chromatolysis.

In this eye the ganglion-cell layer and the rod and cone layer are profoundly degenerated. Apparently some time has passed since the administration of the toxic substance (gliosis).

Dog B.—Received the same drug as Dog A. The optic nerve appears normal. The nerve head resembles that in Dog A; retina, rod and cone elements are not so completely destroyed as in Dog A, but there is again a subretinal albuminous fluid and a clear tendency toward total dissolution of the rod and cone elements; however, these latter elements can still be discerned as shadowy forms. The ganglion-cell layer contains a slight amount of gliosis.

Dog C.—Commercial alcohol given. The nerve and nerve head appear normal. There is a slight amount of albuminous fluid beneath the retina, and also some autolysis of the rod and cone layers. This eye shows early intermediate chromatolysis of the ganglion-cell layer and perhaps beginning autolysis of the rods and cones.

Dog D.—Commercial methyl alcohol given. The nerve and nerve head are apparently normal. The rods and cones are in a fair state of preservation. There is unmistakable evidence that some of the ganglion cells have undergone degeneration.

Dog E.—Formic acid given. This eye is apparently in the same

condition as that in Dog D. The ganglion cells suggest a greater degree of chromatolysis which might result from the same dosage as the previous animal, but a shorter recovery time.

Dog F.—Formic acid given. The nerve and nerve head are normal. The rod and cone layer shows changes similar to those described in the previous two eyes.

Comment.—In summarizing the changes in the acute group, it is evident that the microscopic picture did not vary appreciably with the drug used.

The typical finding appears to be "a practically complete dissolution of the rod and cone elements, with a thickening of the subretinal space because of apparent albuminous accumulation. There is some edema of the ganglion-cell and nerve-fiber layers. The ganglion cells are undergoing acute chromatolysis with dissolution of the cells. Large vacuoles are present in the cytoplasm of many of them. Many of the ganglion cells are reduced to shadow forms."

As regards the optic nerve, some cases presented a normal appearance whereas others showed an edema of the nerve head recognizable by the increased fluid in the spaces in the nerve head and by the retraction of the retina from the choroidal ring.

The changes found in the chronic group corresponded to those in the acute group except that the changes were more pronounced as a whole.

A characteristic description of a chronic case is as follows: "The optic nerve is essentially normal. The rod and cone layer of the retina is completely disorganized, and there seems to be an increased albuminous fluid content. The ganglion-cell layer appears to contain an increased number of glial cells and a diminished number of ganglion cells. Of the few ganglion cells that remain, many are in an advanced stage of chromatolysis. The ganglion-cell layer and the rod and cone layer are profoundly degenerated in this eye."

This description stresses a more profound change and the presence of glial cells.

In drawing conclusions, it seems evident that the animals reacted similarly to the pure methyl alcohol, commercial methyl alcohol, and formic acid. Although there were variations in degree, the clinical pictures are similar. Possibly the variations were due to a difference in tolerance of the animals.

It is evident that the retinal changes are not due to postmortem effects as the eyes were fixed immediately. It is also evident that the predominating changes occurred in the retina, with a certain amount of edema of the optic nerve in a few cases. It seems that the more severe the retinal change, the more evidence is there of edema of the optic nerve.

In comparing the tissue changes found in the acute group with those found in the chronic group, it is obvious that the latter group shows more pronounced pathologic changes. This is manifested by the more extensive and the greater degree of tissue changes. In addition, other findings, such as gliosis, indicate a tissue reaction resulting from prolonged exposure.

This would seem to indicate that the prolonged exposure to the toxin does not materially alter the pathologic changes except to accentuate them and, in addition, cause a tissue reaction characteristic of a process of longer duration.

In summarizing this experimental work, it appears that the findings in this group of cases confirm retinal and optic nerve changes found in other experimental work of a similar nature.

GENERAL PATHOLOGIC CHANGES SEEN IN METHYL ALCOHOL POISONING

General Symptoms of Poisoning.—The symptoms usually exhibited by patients having a toxic reaction from methyl alcohol poisoning vary in intensity, the milder cases showing moderate evidences of intoxication, and the severe cases exhibiting extreme prostration. Usually the toxic symptoms come on in from twelve to twenty-four hours after the inges-

tion of the poison. There is apparently a circulatory disturbance, manifested by the cyanosis and extreme prostration; there is a respiratory disturbance, shown by the reduced number of respirations; and a gastric disturbance, evidenced by nausea and vomiting. The patient complains of pain in the head, limbs, and body, but especially in the epigastrium. Death may come on suddenly as a result of paralysis of the respiratory organs. The heart may continue to beat for some time.

Autopsy Findings (Exclusive of the Eye) Found in the Human.—In general, two conditions combine to form the usual picture. One is a gastro-enteritis of varying severity, the local effect of the poison. The other is a passive congestion of the lungs, brain, and various other organs, and a peculiarly colored fluid blood.

The pancreas, spleen, liver, kidneys, lungs, and gastrointestinal tract all show closely similar signs; namely, edema, hemorrhagic changes, and degeneration of the highly specialized tissues, such as glomeruli, etc.

The influence of methyl alcohol on the central nervous system is similar to that elsewhere in the body, and is manifested by capillary congestion, edema, and patchy degeneration in the neurons. This cellular degeneration is said to occur both in the spinal cord and in the brain. Edema and congestion of the brain and meninges and an increase in the amount of spinal fluid were noted.

Menne[17] reported that the minute alterations observed in the central nervous system (brain and medulla oblongata) consisted of marked subpial and moderate cortical and subcortical interstitial edema, with spotty perivascular and perineuronal extension. Occasional minute focal hemorrhages were seen.

In view of these findings, it is logical to attribute these results in large part to cerebral circulatory disturbances, in addition to the direct action of the toxin.

Blood.—There is a decrease in the number of lymphocytes.

The acidity, electroconductivity, and viscosity are increased, whereas the coagulation time is reduced.

Pathologic Changes in Animal Tissues, Exclusive of the Eye.—The characteristic changes are as follows:

Brain.—The lesions found in the various parts of the cerebrum, the cerebellum, the medulla, and the pons consisted of different degrees of inflammatory and degenerative processes. Macroscopically, the tissues appeared yellowish and glistening; the line of demarcation between the gray and the white matter was not so sharp as in the control animals. In the more prolonged cases the gray matter appeared quite thinned, and the entire picture was one of a nonspecific atrophy.

Microscopically, the ganglion cells were diminished in size and assumed a spindle-like shape. Nissl's granules also were diminished, with brownish pigment scattered here and there. In the most severe cases the parenchyma cells were greatly reduced in number as well as in size. Other nerves besides the optic nerve showed involvement.

Blood.—The chemical reaction of the blood serum was found to be acid. Ruggeri[21] found a considerable increase in the fatty acid and cholesterol content of the blood serum.

Heart.—The earliest cardiac changes began as an edema and progressed to granular degeneration.

Kidney.—The almost constant change in the kidney was a parenchymatous degeneration of the epithelium lining the convoluted tubules.

Liver.—The reaction in the liver was practically always one of parenchymatous degeneration.

Gastro-intestinql System.—The mucous membrane of the stomach was hyperemic, the hyperemia being in the form of islets. Sometimes the membrane was dropsical and yellow in places. Quite often there were hemorrhagic spots and erosions. Some ulcers were the size of a silver quarter. Hyperemia continued to the duodenum and the upper one-fourth of the small intestine.

Comment.—The early symptoms seem to group themselves around a paralysis or depression of both the medulla and the cranial autonomic system, whereas the later symptoms might well be ascribed to the failing functions of the kidney and gastro-intestinal tract. A patient suffering from methyl alcohol poisoning to this severe degree rarely recovers.

The clinical picture is that of extreme prostration and is characteristic of an overwhelming toxemia which affects the entire system.

The tissue changes, as found in experimental animals, are probably of greater value in depicting the injurious effect of methyl alcohol than are the human tissues obtained at autopsy. This is due to the fact that the experimental animal can be more easily controlled and that the tissues have not undergone postmortem changes. This applies particularly to the highly specialized tissues, such as are found in the central nervous system, kidney, etc.

However, the susceptibility of the tissues of animals to wood alcohol must be considered in the evaluation, since there is possibly a wide variation in the effects as compared with man.

It seems evident that the central nervous system—notably the cerebrum—appears to bear the brunt of the attack, it, together with the optic nerve, being the most frequently as well as the most extensively involved organ. Next in frequency, but not necessarily in extent of involvement, are the kidneys, the liver, and the muscles.

In drawing conclusions from the foregoing findings, it is apparent that most of the changes result from the direct effect of the drug. This toxic element, by virtue of its direct effect, may cause degenerative changes in the highly specialized tissues, such as the central nervous system, kidney, liver, etc. An edema, apparently caused by the corrosive action of the poison, results. A circulatory disturbance follows and completes the picture.

CONCLUSIONS

1. There Exists an Uncertainty Concerning Our Present Knowledge of the Action of Methyl Alcohol on the Eye

In reviewing the literature, we are impressed by the diversity of opinion concerning the nature of the ocular pathology. It is surprising that a subject of this scope, which has been the cause of many preventable deaths and blindness, should create so little enthusiasm in the profession, leaving the question as to the exact pathologic process unsolved.

We must admit that the question still is not fully settled. It will remain unsettled until, as has been suggested, some experimenter will examine properly a human eye before post-mortem changes have taken place. The problem should not be limited to this, but should rather include other factors that would throw more light upon the toxicologic process and enlighten us as to changes elsewhere in the body.

If, in addition to the pre-mortem analysis, toxicologic and pathologic analyses were made of all tissues at the moment of death before postmortem changes could occur, our problem would be placed on even a more exact basis. Until a complete analysis, such as has been described, is made, our knowledge as to the exact process and associated pathologic changes is but supposition based upon uncertain factors. Such a study can be done on practically any moribund case without complicating the situation and without much expenditure of time and cost.

2. The Ocular Tissues Show Characteristic Pathologic Changes

In considering this phase of the subject, we must view the eye in its entirety. Ordinarily, we think only of the retina and the optic nerve in this connection.

It may be stated with considerable certainty that we have little or no information regarding any positive pathology in the eye which occurs in methyl alcohol poisoning except the changes in the retina and optic nerve. There are some data

on the choroid, but practically none on other structures of the eye. Autopsy and animal experiments do not mention any pathologic changes related to the problem except an increased acidity of the aqueous and a few isolated instances of ciliary engorgement.

Clinical evidence points to conjunctival and scleral hyperemia and pupillary changes which indicate a break in the reflex arc posterior to the eyeball. No case of iritis, uveitis, cataract, glaucoma, or any other ocular pathologic state has been recorded. A few cases of ptosis and extra-ocular muscle paralysis have been recorded, but these do not apply to the eyeball directly. In the two cases reported by the author no change that could have been attributed to the poison was observed, nor any structure affected except the retina, choroid, and nerve.

Choroid.—A study of the microscopic data available seems to indicate the presence of vascular congestion and edema. The vessels are distended, and the choroidal structure shows signs of edema of variable degree. This is usually more pronounced when the adjacent retina is involved, and the degree of change is in proportion to the retinal change. There is, as a rule, little evidence of an inflammatory reaction present. There is no apparent injury to the vessel structure.

Retina.—From the description of the changes in the retina one may conclude that the effect of the poison first makes itself evident in the ganglion cells. After this the inner nuclear layer, later the outer nuclear layer, and finally the rod and cone layer, degenerate. In cases where the layer of ganglion cells is greatly changed, other elements of the retina are also considerably affected.

The general picture of changes in the retina, in addition to the degenerative process, shows edema. This is shown in the thickening of the different layers, in separation of cells, in the appearance of crevices and spaces, and in dilatation and thickening of Mueller's fibers. The picture found in the nuclear layers completes this impression of dropsy, because

here the cells are not only markedly separated, but appear as if a general current transposed them into the neighboring layers.

Since the degeneration is not always connected with dropsy, one should not conclude that all these phenomena were conditioned by it, for in places the dropsy is absent, but the degeneration is present. It is evident, moreover, that at times the dropsy became absorbed, or diminished, for in more chronic cases it is present less often than in acute conditions.

Optic Nerve.—There is definite evidence of degenerative changes occurring in the optic nerve. Accompanying these degenerative changes, there are signs of edema to a variable degree.

3. The Various Ocular Changes are Similar in Nature and All Tissues Affected Become Involved Simultaneously

That all the pathologic changes found in the ocular tissues are similar in nature is evident upon studying the data available. Although the change may be found to be more pronounced in the retina than in the optic nerve, or vice versa, the same type of pathologic change exists in both.

The most conspicuous changes are degeneration and edema. These have been described in the previous section, and it is logical to believe that whatever the cause of the process may be, it produces the same tissue changes and reaction in the retina as in the optic nerve. This reaction would naturally be more evident in the microscopic section of the retina than in the nerve, because of the nature of the highly delicate tissue present in the retina, its less compact arrangement, and other anatomic features which are so different from those found in the optic nerve. In considering these anatomic and physiologic differences, plus the possibility of earlier postmortem degeneration, it is only logical to expect more pronounced microscopic changes in the retina than in the optic nerve, especially if the process is early. It is, therefore, evident that in analyzing the respective findings

we are dealing with a similar process. That the process involves both the retina and the optic nerve simultaneously seems possible, judging from the data available.

In spite of all the clinical evidence to show that the optic nerve is involved first and the process is a descending nerve involvement, there is also evidence, chiefly microscopic, to show that the retina is likewise involved. It cannot be denied that in weighing all the microscopic evidence, both animal and human, we have conclusive proof that the retina shows pathologic changes; this in spite of the negative results of certain reliable workers. Until it can be proved that these negative results are correct, the author will assume that the retina does show pathologic changes. This contention is based upon the animal work reported in the literature, human tissue findings, the author's experimental results, and the lack of adequately reported experimental data to prove otherwise.

It is possible that the processes in the retina and optic nerve are not dependent upon one another. It has been observed that the degenerative changes appear simultaneously in the optic nerve and in the retina, and are noticed within a few hours, a condition which suggests the independence of both processes. Degeneration has been found in the oculomotor and other nerves, which indicates that an affection of nerves independent from the retina is possible in such cases. In some instances, the prevailing affection was noticed in the optic nerve and was of a descending character, and not the opposite, as should have been expected if the retina were primarily involved, although the ascending atrophy would not show at an early stage. Other arguments point to an independent retinal involvement.

Thus, one can see that in poisoning with methyl alcohol, both retinal and optic nerve changes may take place simultaneously, a situation which brings reconciliation to both extreme views expressed by various authors. It is difficult to admit that there is a mistake from either side, but the

existence of two situations, one dependent upon the other, is hard to imagine.

In considering all the factors here described, and after weighing all the evidence available, it is logical to conclude that the predominating retinal pathologic changes could be explained on the basis of the structure of the retina. Its anatomic and physiologic properties would explain the greater sensitivity to the action of the toxic agent.

When we consider the nature of the tissues involved, it would seem that, even though both the retina and the optic nerve are exposed to the toxic element simultaneously, the initial injury would be more pronounced in the ganglion cells of the retina, and the microscopic picture would show the predominating changes in the retina.

It is not logical to conclude that the optic nerve changes seen with the microscope are the result of the injury to the ganglion cells. It is more reasonable to believe that these changes found in the optic nerve in the acute cases are due to a local injury to the nerve tissue by the toxin and is similar to the injury to the ganglion cells.

It is not possible for an ascending degeneration to occur in the optic nerve in the acute cases because the time element would not permit it to manifest itself so soon. It is, of course, evident that later, when the optic nerve atrophy is present, the ascending atrophic process accounts for some of the nerve changes. At this stage, the optic nerve atrophy is represented by both atrophy originating in the nerve and that occurring as the result of the degeneration of the ganglion cells.

Before concluding the section dealing with the pathologic changes, it should be reemphasized that the previously described pathologic changes are fundamentally degenerative changes. These degenerative changes occur not only as the result of the action of a toxic substance, but as the result of a metabolic disturbance which interferes with the nutrition of the tissue. It has been demonstrated by Birch-Hirschfeld[29]

and others that these degenerative changes occur in the retinal tissue a few hours after the nutrition to the retina has been suspended. By interfering with the circulation for but fifteen minutes, Guist[31] demonstrated the presence of degenerative changes in the retina.

This being the case, we must consider this factor in interpreting the pathologic changes reported. In the case of the microscopic reports on human eyes, evidence points to the fact that in most instances the eyes were not fixed immediately after removal. This is based upon the report of MacDonald,[16] the author's cases, and the lack of a positive statement as to the time of tissue fixation in the other cases reported. It must be accepted, therefore, that at least some of the degenerative changes reported can be attributed to postmortem processes. This does not detract from the fundamental fact that methyl alcohol will also produce such changes, because the author took precautions to prevent postmortem changes in his animal work by fixing the material immediately after death.

4. The Eye Changes are but One Part of the Pathologic Picture, and the Whole Organism is Involved

It would seem unnecessary to make this point, but due to the fact that some may regard the condition as a specific affection of the eye, it seems advisable to point out the general pathologic changes that are associated with methyl alcohol poisoning.

Frequently the lesions of the eye have been so conspicuous as to mask the other manifestations of the poison of methyl alcohol. The pathologic conditions arising from these associated effects may, however, be just as constant as, and possibly more important than, the changes taking place in the eye. Also, it is possible that an individual may suffer from methyl alcohol poisoning in severe degree and still show no eye changes, just as meningeal lesions are no longer considered essential for the diagnosis of meningococcus-infections.

That the eye symptoms are but a local manifestation is evident when one considers the subjective symptoms. In addition to the visual changes, there are signs of profound shock to a greater or less degree. The circulatory, respiratory, digestive, cutaneous, and nervous symptoms all indicate a complete systemic involvement.

The findings at autopsy all indicate much the same type of pathologic change as is found in the eye.

The central nervous system shows, in addition to the circulatory disturbance, evidence of contact with a toxic substance which produces degenerative changes and edema. These degenerative changes are more pronounced in the highly specialized ganglion cells, a condition that is to be expected because of the sensitivity of these cells to disturbance of their chemical structure. Similar changes, but in a less marked degree, are found in the nerve-fibers, both central and peripheral.

The specialized cells of the kidney, liver, etc., manifest pronounced changes in comparison to less specialized tissues, such as muscle tissue.

The gastro-intestinal tract shows signs of irritation, caused by a direct and repeated contact with the toxin.

The blood findings likewise show changes indicating a toxic reaction. Especially noteworthy is the presence of acidosis in these cases.

It seems evident, therefore, that the entire organism is affected, although the highly specialized tissues give greater evidence of pathologic changes.

5. Methyl Alcohol is Broken Down in the Body, Forming Toxic Substances which cause Pathologic Changes

When considering the action of methyl alcohol in the human body, the following factors seem evident:

That individual susceptibility varies markedly, and that some persons are practically immune, whereas others present a definite idiosyncrasy to it.

Tolerance is not acquired to any degree.

Impurities are not an influencing factor.

Undoubtedly the basic factor in causing the toxic action is the inability of the body to oxidize the methyl alcohol to carbon dioxide and water, as takes place with ethyl alcohol. Evidence shows that the methyl alcohol enters very little into the tissue metabolism. The body does, however, attempt to oxidize it, but does not follow the usual course. Instead, it deviates, forming other chemical compounds which apparently are more toxic than the methyl alcohol.

The slow elimination of the drug is proof that the body has difficulty in oxidizing methyl alcohol, and the urinary findings, which show methyl alcohol and formic acid are further evidence that the body has difficulty in coping with the toxic agent.

That methyl alcohol is broken down into other chemical products is evident, and one or more of these products may be the cause of a toxic reaction greater than that caused by methyl alcohol. Formaldehyde may be formed, and there is definite proof that formic acid is formed. Even though formic acid may be formed slowly, it seems possible that it is present for a sufficiently long time in the body to be brought into contact with all the tissues, and a momentary contact may be all that is necessary. That it is toxic in the living body has been substantiated by the author's experiments, in which formic acid produced at least as great a reaction in the ocular tissues as did methyl alcohol.

The various tests show that methyl alcohol is in contact with the tissues for a considerable time after ingestion, which undoubtedly is a possible factor in producing changes of a pathologic nature. The fact that the toxic action (at least the eye pathology) does not become evident until some hours after the drug has been ingested suggests that some additional factor must be introduced. If it were the alcohol alone, the toxic effect would be manifested at once. This points to the fact that the slowly formed decomposition

products may be a factor in producing, at least, the eye pathology.

Cumulative effect may be a factor in producing toxic changes, but cases are reported in which only one exposure produced alterations, thus eliminating the possibility of cumulative changes serving as a major contributing cause.

Acidosis may contribute an additional toxic element; it could also be partially responsible for some of the tissue changes.

That the toxic action is wide-spread throughout the entire system is evident. We know that methyl alcohol is distributed to all the tissues, and likewise any other toxic element would be similarly distributed. The more highly differentiated tissues, although showing more pathologic change, do not apparently receive more exposure than any other tissues.

It, therefore, seems that the toxic factors which produce the pathologic tissue change could be the decomposition product or products acting with or without the methyl alcohol. Acidosis is also an accompanying agent of more or less importance. Formic acid is apparently one of the important products of oxidization which is responsible, acting either alone or in combination with the other toxic elements.

6. The Pathologic Change is the Result of the Direct Action of the Toxic Substance on the Tissues

In considering the nature of the toxic action on the tissues we definitely enter the field of supposition. The explanation offered must be based upon whatever evidence is at hand. The following statements appear to the author to be logical deductions based upon what information there is available.

It has been demonstrated that the toxic substances in methyl alcohol poisoning are very diffusible and penetrate the eye readily. The toxic substances come in direct contact with all the tissues of the eye, and, by this direct action, produce a variable pathologic effect, depending upon the type of tissue. In the case of the highly differentiated elements, such as are

found in the retina and the optic nerve, the effect of the exposure to the toxin is more pronounced. Although this highly sensitized tissue, such as the retina and the optic nerve, may not have a special affinity for the toxic substance, there is a possibility that, because of the high lipoid content or for some other structural or chemical reason, a more pronounced chemical effect is produced than occurs in the less specialized tissue, such as the supporting connective tissue, uveal tissue, etc. It is a known fact that highly developed tissues are always found to be more susceptible to this type of injury than are other types of tissue. It is highly probable that the toxic element in some way interferes with the metabolism of the cell, and because of its sensitivity to such a disturbance, degeneration takes place in the cell.

This interference with the metabolism of the cell may be of the nature of oxygen famine or some similar chemical process.

Beyond a few isolated facts, little is known of the mechanism of metabolism of the retina. The retina certainly has considerable oxidizing powers, and the oxidative capacity is said to increase in light adaptation. In comparison with other tissues it has a marked power of glycolysis. A considerable amount of lipoid substance is also present.

Quoting Duke-Elder[30]: "Its destruction is easy, partly because of the delicacy and complexity of its structure which rapidly falls a victim to noxious influences, and partly because of the intensity of its metabolism which is unable to support the deprivation of essential supplies with impunity for any length of time. It will be remembered that, although the metabolism of the retina is still largely a mystery, we do know that it has a very high oxidative capacity and a glycolytic activity of unusual intensity, about twice that of the iris, which is approximately equal to that of muscular tissue. Once an adequate supply of oxygen is cut off, or once the tissue is exposed to the action of leukocytes, exudates, or bacteria, death rapidly sets in.

"In the absence of toxic elements, the destruction of the tissue is by autolysis, while in the presence of toxins or inflammatory processes, heterolysis occurs. As a result, the retina rapidly becomes swollen and opaque and eventually suffers total atrophy, only a reticulum of the supporting framework of nerve tissue and strands of the connective tissue associated with the blood-vessels remaining, while glial proliferation is stimulated.

"Autolysis occurs when, in the injured or dying tissues, anabolism cannot maintain its equilibrium with catabolism, with the result that acids are formed in excess. The enzymes, which in the normal alkaline retina take part in its metabolism, continue to break up metabolites to form acid products which cannot be dealt with, the increased osmotic activity of which leads to the imbibition of water and a swelling and translucency of the tissues. The proteolytic enzymes then begin to act, hydrolyzing the intracellular proteins into smaller and smaller fragments, and converting the large molecular aggregates into simpler products, which diffuse away, eventually leaving only the supporting tissue behind."

It has been shown by Goldschmidt[8] and, Oguchi[32] that, as a result of exposure to the toxic factors of methyl alcohol, the oxidative processes in the retina are much impaired and its respiratory activity lowered, so that the metabolism may be reduced by 40 to 50 per cent. Goldschmidt[8] also concluded that the damage is greater when the retina is exposed to light, a view put forward also by Schanz[23] and Schieck,[33] but not universally accepted.

It seems to be fairly well established, therefore, that the retina and the optic nerve are sensitive to metabolic disturbance, and that such a disturbance leads to degenerative changes.

It is possible that the toxin, acting on the terminal capillaries, causes a vasoconstriction, and because of the diminished blood supply to the trophic centers the nutrition of the retinal cells is interfered with and results in a metamorphosis of the cells.

Acidosis has been suggested as a factor contributing to the interference with the tissue metabolism. Titration of the aqueous has demonstrated the presence of acidosis in the eye.

The injury to the cells may not only be metabolic—it may also be due to a direct corrosive chemical action.

Irrespective of the mechanism, the toxic substance produces a degenerative change in the tissue, and especially in the highly differentiated tissue, such as the cells in the retina and, to a lesser degree, the nerve-fibers. That this is not an inflammatory change is evident because of the lack of an inflammatory reaction.

The tissue cells are not all affected equally, because injury seems to occur in patches, with intermediate areas of less affected cells. This applies to both the retina and the optic nerve. Such an explanation would account for the scattered scotomas found on perimetry study. Apparently the papillo-macular bundle is especially vulnerable because of the frequent occurrence of central scotomas.

The degree or extent of the degenerative process in the retina and the optic nerve is in proportion to the intensity of the toxic element and the susceptibility of the individual.

Edema of the nerve tissue and supporting tissue is the result of both an irritative reaction of the tissue to the toxic substance and the degenerative process.

According to Duke-Elder,[30] an essential factor which produces edema is an alteration of the molecular constitution of the retinal tissues whereby large protein complexes are broken down into smaller entities, as occurs in toxemia. In toxemia the tissues are starved because of the loss of their nutrient blood supply or surfeited with the accumulated waste products of their deranged metabolism, and in consequence they imbibe fluid freely not only from the retinal capillaries, but from the choriocapillaris and probably from the vitreous as well. In its earlier stages the process is reversible, but if the tissue enzymes, acting freely in the direction of catabolism in the acid media created by the

anoxemic state, continue to break down the tissue proteins, irreparable damage may be done by autolysis, until eventually a condition of complete atrophy results, the retina being represented only by its more resistant supportive elements.

Edema leads to compression of the nerve tissue and may serve as an important etiologic factor in causing the initial visual loss by compression of the unaffected and partially affected nerve elements, thus resulting in temporary interruption of vision. When the edema begins to subside, the nerve-fibers gradually resume their function and vision improves in proportion to the number of viable cells remaining. The secondary visual failure is the result of further degeneration of the partially degenerated fibers that did not succumb to the original toxic action, but were further injured by the effect of the edema.

As a rule, when the process is confined to the inner layers, the edema may subside without inflicting damage; but once the internuclear layer is seriously involved, permanent injury results.

The edema also may lead to circulatory disturbances by causing a stasis in the vessels supplying the retina and optic nerve.

The inner (cerebral) retinal layers are nourished by the retinal vessels in the same manner as is the central nervous system; the outer layers are avascular, and, being a sensory epithelium, they receive their nourishment by diffusion from the choroid.

In the cerebral layers of the retina the blood-vessels do not come into direct contact with the nervous tissue, but are insulated from it by perivascular glial sheaths through which fluid interchange takes place, and by means of which lymphatic drainage is effected. It can readily be seen how, under these conditions, the edema would produce circulatory stasis and would be an additional factor in causing a disturbance in the metabolism of the cerebral layer of the retina.

This circulatory interference is also evident in the choroid

and supporting structure of the optic nerve, and is responsible for the hemorrhages which are occasionally found in the optic-nerve sheaths.

This, therefore, is a statement of the author's interpretation of the process which leads to the pathologic changes in the eye in methyl alcohol poisoning. After weighing the various facts at our disposal, such a conclusion seems to be one explanation of the intricate processes which take place. It is given with much trepidation, although a work of this nature would not seem complete without such an attempt. It may be said in conclusion that it can stand until proved incorrect; even in that case it will have served a purpose until additional research work is done in this as yet little understood field.

REFERENCES

1. Birch-Hirschfeld: Arch. f. Ophth. **50**: 1, 1900..
2. Birch-Hirschfeld: Deutsche med. Wchnschr. **46**: 311, 1920.
3. Bongers: Arch. f. exper. Path. u. Pharmakol. **35**: 426–429, 1895.
4. De Schweinitz, G. E.: Text Book of Ophthalmology, Philadelphia, 1896.
5. Friedenwald, Jonas: Pathology of Eye, 1932.
6. Friedenwald, H.: J.A.M.A. **137**: 1450, 1901.
7. Friedenwald and Felty: 1920. Not published.
8. Goldschmidt, M.: Deutsche Ophth. Gesellsch. pp. 129–139, 1922.
9. Harrop and Benedict: J.A.M.A., June 3, 1920.
10. Henderson, Y., & Haggard: New York Chem. Catalog Co., 1927.
11. Holden, Ward: Arch. f. Augenh. **40**: 351–353, 1900.
12. Holden, H.: Arch. Ophth. **28**: 125, 1890.
13. Igerscheimer & Verzar, R.: Arch. f. Augenh. **75**: 27–35, 1913.
14. Kazas, I. I.: Chem. Abstr. **7**: 3794, 1913.
15. MacDonald: Cited by Scott and others (26).
16. MacDonald: Concilium (International Congress), 1929.
17. Menne: Arch. Path. **26**: 77–92, 1939.
18. Pick, L., & Bielschowsky, M.: Berl. klin. Wchnschr. **49**: 888–93, 1912.
19. Placet: Textbook on Toxicology of Methyl Alcohol, Paris, 1912, No. 335, p. 49.
20. Pohl, J.: Arch. f. exper. Path. u. Pharmakol. **31**: 281, 1893.
21. Ruggeri: Arch. di antrop. crim. (etc.) Torino, 8: (Supp.) 91–103, 1916.
22. Rymowitsch: Dissertation, St. Petersburg, 1896.
23. Schanz, F.: Ztschr. f. Augenh. **43**: 73–86, 1920.
24. Schwartz: New York M. J., p. 588, 1920.
25. Schwarzkopf, G.: Ztschr. f. Augenh., **48**: 317, 1922.
26. Scott, E., Helz, M. K., & McCord, C. P.: Am. J. Clin. Path., p. 311, July 1933.
27. Tyson & Schoenberg: Tr. Am. Ophth. Soc. **13**: 146, 1912.
28. Voltz, W., & Dietrich, W.: Biochem. Ztschr. **40**: 15–28, 1912.

29. Birch-Hirschfeld: Arch. f. Ophth. **52**: 358, 382, 1901.
30. Duke-Elder: Text Book, 3: 3021.

31. Guist: Duke-Elder Text Book, **3**:3021.
32. Oguchi: Acta S. O. Jap. **36**: 155, 1932.
33. Schieck: Arch. f. Ophth. **54**: 458, 1902.

ADDITIONAL REFERENCES

Abbott, S. W.: Boston M. S. J. **147**: 63, 1913.
Adams, F.: Arch. f. Chem. u. Mikrosk. **7**: 20–25, 1915.
Adler, H.: Wien. med. Wchnschr. **48**: 1401–1407, 1898.
Afanissejew: Ziegler's Beitr. **3**: 443.
Agduhr, E.: Arch. internat. de pharmacodyn. et de therap. **59**: 269–294, 1938.
Albaugh: Mod. Med. **1**: 300.
Alder, P., Buschke, W., & Gordenoff, T.: Arch. internat. de pharmacodyn. et
    de therap. **59**: 416–430, 1938.
Allport, F.: Ophthalmology, **12**: 618.
Alyardik, P. A.: Vestnik Obshtsh. Hig., Sudeb. i Prakt. Med., Petrogr.
    51: 459–465, 1915.
Andrews, C. L.: Med. Soc. N. Jersey, Orange, **22**: 288–294, 1925.
Armstrong, M. D.: Maritime M. News, Halifax, **15**: 448–450, 1903.
Aronshon: Berl. klin. Wchnschr., p. 751, 1892.
Asser, E.: Ztschr. f. exper. Path. u. Therap. **15**: 322–334, 1914.
Atchinson, P. J.: N. Y. State J. Med. **5**: 127–129, 1905.
Atkinson: J. Am. Pharm. A. **17**: 28.
Audibert, Etienne, & Raineau, André: Indust. & Engin. Chem. **20**: 1105, 1928.
Ayres, S. E.: Am. J. Ophth. **2**: 91–97, 1885.
Bab, W.: Berl. klin. Wchnschr. **56**: 995, 1919; abst. J.A.M.A. **74**: 637.
Bachmann, R. A.: U. S. Navy M. Bull. **3**: 33–36, 1909.
Baer, George: Arch. f. Physiol. **6**:283–296, 1898.
Ball, J. H.: Homoeop. Eye, Ear & Throat J., N. Y. **11**: 325–333, 1905.
Ballet et Dutil: Centralbl. f. Nervenh. 21, 1897.
Barbash, S.: J.A.M.A. **78**: 430, 1922.
Baskerville, Chas.: New York M. J. **3**: 580–583, 1920; N. Y. State Factory
    Investigation Com., 2nd Rept. **2**: 924, 1913; Am. J. Pharm. **92**: 904–908,
    1920.
Battelli & Stern: Compt. rend. Soc. de biol. **68**: (No. 1) 5, 1910.
Bell, E. E.: Tr. N. Hampshire M. Soc. 259–269, 1902.
Benetal: New York M. J. **111**: 16, 19, 1920.
Benoit: Ophthalmology, **8**: 433, 1911.
Berkley: Brain, 1895.
Bernhard, C. G., & Goldberg: Skandin. Arch. f. Physiol. **67**: 117–128, 1933.
Bertarelli: Ann. d'ig. **42**: 665–676, 1932; **44**: 729–731, 1934.
Betts, S.: Navy Bulletin, **13**: 791.
Bielschowsky: Berl. klin. Wchnschr. **49**: 859, 1912.
Bigelow: New England M. J. 198–227.
Bildsten: Biochem. Ztschr. **146**: 361–369, 1924.
Bills and Maukin: J. Comp. Psychol. **1**: 495–505, 1921.
Birch-Hirschfeld: Klin Monatsbl. f. Augenh. **39**: 682, 1900; Ztschr. f. Augenh.
    35: 1–12; Ber. ü. d. Versamml. d. ophth. Gesellsch., p. 48, 1900; Ber.
    ü. d. Versamml. d. ophth. Gesellsch. 1900; **28**: 48–56, 1901; Arch. f.
    Ophth. **54**: 68, 1902; Deutsche med. Wchnschr. **46**: 311, 1920.
Birch-Hirschfeld & Stimmel: Arch. f. Ophth. **90**: 1380, 1915; Med. Klin.
    12: 227–230, 1916.
Black, G. M.: New York M. J. **54**: 287, 1891.
Blegvad, O.: Ugesk. f. Laeger, **82**: 1575, 1920.
Bodkin, H.: South African M. Rec., Cape Town, **24**: 208–209, 1926.
Boeseken and Waterman: Chem. Weekbl. **9**: 694–696, 1912.
Bogue: Vermont M. Month. **12**: 31, 1906.
Boyle: See Baskerville.

Brown, E. V. L.: Tr. Am. Ophth. Soc. **12**: 517–521, 1909–1911.
Brown, Ralph, & Galloway, A.: Indust. & Engin. Chem. **20**: 960, 1928; ibid. **21**: 310, 1929; ibid. **22**: 175, 1930.
Bruckner: Zentralbl. f. Gewerbehyg. **1**: 17–20, 1924.
Bruner, W. E.: Ophth. Rec. **13**: 48–51, 1904.
Bruns, H. D.: New Orleans M. & S. J. **10**: 759, 1886–87.
Buchner, Fuchs, & Megele: Arch. f. Hyg. **40**: 347, 1901; Arch. f. Hyg. **40**: 247–274, 1901.
Buerger: Chem. Ztg. **36**: 524, 1912.
Buller, F.: Montreal M. J. **33**: 29–38, 1904.
Buller and Wood: J.A.M.A. **43**: 972, 1058, 1117, 1213, 1289, 1904.
Burcham, James D.: J.A.M.A. **96**: 884, 1931.
Burger: Berl. klin. Wchnschr. **49**: 1705, 1912.
Burhans, E. C.: Illinois M. J. **57**: 260–263, 1930.
Burnett, S. M.: Ophth. Rec. **11**: 309, 313, 1902; Therap. Gaz. **17**: 801–807, 1901.
Busch, A.: J. f. Psychol. u. Neurol. **17**: 63–89, 1910; **18**: 36, 1911.
Callan: New York Acad. Med. Report, 1899.
Campbell, J. A.: J. Ophth., Otol. & Laryngol. Sept., 1915.
Carhart, W. M.: Am. Med. Burlington, Vermont, & New York, **3**: 176, 1908.
Chapin: J.A.M.A. p. 524, January, 1922.
Cheatham, W.: Louisville J. S. & M. **12**: 27, 1905–6.
Claiborne, J. H.: Arch. Ophth. **49**: 329–332, 1920.
Colburn: Ophth. Rec. **8**: 12, 1899.
Cololian: J. de physiol. et de path. gén. **3**: 535.
Comora, A.: Med. Rec., New York, **97**: 764, 1920; New York M. J. **111**: 588.
Conboy, D.: J. Mich. M. Soc., Detroit, **3**: 536–538, 1904.
Cornalba: Boll. chim. farm. **51**: 37–38, 1912.
Cowper: Ophth. Rec. **25**: 452, 1915.
Cutler, C. W.: Med. Press. London, n.s., **109**: 438–440, 1920; New York M. J. **111**: 585, 1920.
Cutten, G. B.: J. Inebriety, Bost., **30**: 17–27, 1908.
Cuttler, Norris: Arch. Ophth. **49**: 444–447, 1920.
Dalen, A.: Allm. sven. Läkartidn., Stockholm, **3**: 673–683, 1906.
De Bono, F. P.: Arch. di ottal., Palermo, **9**: 130–142, 1901–2.
Dehio: Centralbl. f. Nervenh. u. Psychiat. **18**: 111, 1895.
Déjérine & Thomas: Compt. rend. Soc. de biol., May 1, 1897.
Denis, W., & Aldrich, M.: J. Biol. Chem. **44**: 203, 1920.
Derome, W.: Union méd. du Canada, **56**: 501, 1927.
De Schweinitz, G. E.: Ophth. Rec. **10**: 289–296, 1901; Bowman Lecture, 1923; Tr. Am. Ophth. Soc. **12**: 523, 1911.
De Wecker, L.: J. Eye, Ear & Throat Dis., Balt., **2**: 136–139, 1897.
Dogiel: Arch. f. mikr. Anat. **40**: 34.
Downing, J. M.: J. Iowa State M. Soc. **12**: 446–449, 1922.
Dron, A.: Lyon méd. **15**: 152–159, 1874.
Dron, Gustave: De l'iritis, Paris, No. 129, 32 pp., 1880.
Druault: Trav. de laborat. d'opht. de l'Hôtel-Dieu, Paris, 1900.
Dublin, L., & Lieboff, P.: Bull. 306, H. S. Labor. Statis. p. 31, 1922.
Dujardin-Beaumetz: Compt. rend. Acad. d. Sc. **96**: 1557, 1883.
Dujardin-Beaumetz & Audige: Bull. et mem. Soc. de therap. **2**: 86–142, 1876. Bull. gén. de therap. **79**: 210–265, 311, 357, 404, 1875.
Dumas and Peligot: New York M. J., p. 580, 1920.
Dunlap, K.: Psychobiology, **2**: 187, 1920.
Dunn: Virginia M. Semi-Monthly, January 25, 1901.
Egami, F.: Compt. rend. Soc. de biol. **129**: 1168–1170, 1939.
Egg, C.: Schweiz. med. Wchnschr., **5**: 57.
Eisenberg: Am. J. Pub. Health, **7**: 765, 1917.
Eleonskaja, V.: Russia ophth. J. p. 40, 1920.

Elhart, W., & Orth, O. S.: Anesth. & Analg. **14**: 15–19, Jan.–Feb., 1935.

Elvove, E.: J. Indust. & Engin. Chem. **9**: 295–297, 1917.

Eversole, G. E.: Boston M. & S. J. **169**: 933 1913.

Ewing: Arch. f. Neurol. & Psycho-path., **1**: 3, 1898.

Felletar, E.: Pest. med.-chir. Presse, **47**: 215, 223, 231, 1911.

Fenton, R. R.: Northwest. Med. **19**: 22, 1920.

Flury, F., & Wirth, W.: Arch. f. Gewerbepath. u. Gewerbehyg. **7**: 221–226, 1936.

Foerster, R.: München. med. Wchnschr. **59**: 248–251, 1912.

Foster: Biol. Zentralbl. **40**: 431, 1911.

Foucher: Montreal M. J. or Union méd. du Canada, **33**: 161, 1904.

Fradkine: Clin. Opht. **23**: 382.

Franceschi, G.: Boll. chim. farm. **51**: 325–329, 1912; ibid. **59**: 409, 497–551, 1920. Gior. di farm. **61**: 145–52, 1912.

Fridenberg, Percy: Tr. Am. Ophth. Soc. **12**: 513–525, 1910.

Friedenwald, H.: Bull. Johns Hopkins Hosp., February, 1902.

Friedenwald, Jonas: Tr. A. Am. Physicians, **26**: 61, 1911.

Friedenwald, Julius: N. Y. State Factory Investigation Com., 2nd Rept., **2**: 924, 1913.

Fuchs, A.: Ophth. Literature, p. 278, 1921.

Fuhner: Arch. f. exper. Path. u. Pharmakol. **51**: 1.

Gerbis: München. med. Wchnschr. **61**: 897, 1914.

Gettler: J. Biol. Chem. **42**: 311, 1930.

Gettler, A. O., & St. George, A. V.: Am. J. Pharm. **90**: 280–284, 1918; J.A.M.A. **70**: 145, 1918.

Gibbs, H. D.: Philippine J. Sc. **7**(A): 57–75, 1912.

Gifford, H.: Ophth. Rec. **8**: 441–445, 1899; ibid. **10**: 342–344, 1901; ibid. **15**: 274.

Goldflam, S.: Klin. Monatsbl. f. Augenh. **64**: 684, 1920.

Goldflam, S.: Abst. Am. J. Ophth. **4**: 316, 1921.

Goldschmidt: Ztschr. f. Augenh. **48**: 142, 1922.

Goldsmith: Weyl's Handbuch, **8**: 830.

Golovin, S.: Vestnik oftal. **32**: 453, 1915.

Golperin, S. S.: Mosk. M. J. **4**: 2, 49–53, 1924.

Gradinesco, A., & Degan C.: J. de physiol. et de path. gén. **32**: 363, 826, 1934.

Gradinesco, A., & Palmbert, H.: J. de physiol. et de path. gén. **29**: 45–51, 1931.

Greenburg, L., Mayers, M. R., Goldwater, L. G., & Burke, W. G.: Indust. Hyg. & Toxicol. **20**: 148–154, 1938.

Grignolo, F.: Klin. Monatsbl. f. Augenh. **15**: 157, 1913; Zentralbl. f. Biochem. u. Biophys. **14**: 889.

Gruening, E.: Festschr. z. 40. jsrh. Stiftungsfeier d. Deutsche Hosp., N. Y., 447–483, 1919; Arch. f. Ophth., p. 332, July, 1910; Tr. Am. Ophth. Soc. **12**: 522, 1911.

Grumme: Fortschr. d. Med. **35**: 164, 1917–18.

Haggard: J. Biol. Chem. **59**: 753, 1924.

Haggard, H., & Greenberg, L.: J. Pharmacol. & Exper. Therap. **52**: 161, 1934; ibid. **66**: 479–493, 1934.

Hale: J.A.M.A. **37**: 1450, 1901.

Hall: Tr. Indiana M. Soc. **46**: 330–334, 1895.

Hallberg: Am. M. J. p. 1215, 1904.

Haller, W. G.: J.A.M.A. **95**: 816, 1930.

Hamalainen, R., & Tersakele, H.: Tr. Am. Acad. Ophth. **6**: 260–266, 1929.

Hamburger: München. med. Wchnschr. p. 141, 1918; abst. Klin. Monatsbl. f. Augenh. **60**: 703.

Hamilton, Alice: The Macmillan Co., 1925, p. 42; Rept. to the Commission of Labor Statistics.

Hammarsten: Physiol. Chem. p. 629, 1908.

Hanson, F. B., & Heys, F.: J. Hered. **18**: 345–350, 1927.
Harboe, J. F.: Norsk. mag. f. laegevidensk. **81**: 379, 1920; ibid. **74**: 1552, 1920.
Harbridge, D. F.: Ophth. Literature, **18**: 361–365, 1922.
Harlan: Ophth. Rec., February, 1901.
Harnack, E.: Deutsche med. Wchnschr. **38**: 258–361, 1912; München. med. Wchnschr. **59**: 1941–43, 1912.
Harrop: J.A.M.A. **74**: 25.
Haskell, C., Hillman, S. P., & Gardner, W. R.: Arch. Int. Med. **27**: 71, January, 1921.
Hausmann, W.: Oesterr. San.-Wes. **24**: 181–185, 1912.
Hawes, A. T.: Boston M. & S. J. **153**: 525, 1905.
Hawk, P. B.: Physiological Chemistry, Ed. 6, p. 526.
Heagey, F. W.: Nebraska M. J. **6**: 316, 1921.
Heckel, E. B.: Am. J. Ophth. **5**: 293, 1922.
Heilbronner: Monatschr. f. Psychiat. u. Neurol. 3 u. 4, 1898.
Herbert, J. P.: Am. Med. **3**: 300, 1902.
Hermann: Beitr. z. chem. Physiol. u. Path. **6**: 130, 1908.
Herrick, W. W.: Arch. Int. Med. **23**: 409–418, 1919.
Hesse, E.: Ztschr. f. Augenh. **89**: 51–57, 1936.
Hirschberg, J.: Berl. klin. Wchnschr. **49**: 247–251, 1912.
Hirschberg, T.: Brit. M. J. **2**: 810, 1897.
Holden, Ward: Arch. f. Ophth. **28**(2): 129, 1899.
Hollander: Chem. Zentralbl. **1**: 671, 1910.
Holloway, T. B.: Tr. Ophth. Sect., A.M.A., page 352, 1923.
Hooper: Report of Pharm. College of London, **18**: 189, 1904.
Hopden: Report of Comm. for Prevention of Blindness, 1915.
Hoppe, F. A., & Seyler: Ztschr. f. Biol. **90**: 433–466, 1930.
Horbaczewski: Oesterr. San.-Wes. **2**: 27–29, 1910; Oesterr. chem. Ztg. **14**: 139–41, 1911.
Hotz, F. C.: Ophth. Rec. **8**: 561, 1899.
Howard, Charles H.: Report of New Hampshire State Board of Health, December, 1930.
Hubbard, S. D.: New York M. J. **3**: 16, 1920.
Hufferd, R. W.: J. Am. Pharm. A. **21**: 548, 1932.
Hull and Mink: U. S. Navy M. Bull. **7**: 291–294, 1914.
Hunt, Reid: Indust. & Engin. Chem. **17**: 763, 1925; Bull. Johns Hopkins Hosp. 213, 1902.
Hurst, V. R.: Am. J. Ophth. **4**: 277, 1921.
Hynson, H. P., & Dunning, H.: Pharm. Rec. **19**: 54–56, 1901.
Hyson, H. H.: Tr. Am. Ophth. Soc. **13**: 146–161, 1912.
Igerscheimer & Verzar: Zentralbl. f. Biochem. u. Biophys. **15**: 942, 1912; Arch. f. Augenh. **75**: 27, 1914.
Iida, Y.: Jap. J. Gastroenterol. **13**: 175–178, 1936.
Ionescu Matiu, A., Popesco, C., & Popa, I.: Bull. Acad. de méd. de Roumanie, **3**: 511–524, 1938.
Isaacs: J.A.M.A. **75**: 718–721, 1920; Cincinnati M. J. **1**: 251–253, 1920; Ohio State M. J. **17**: 470, 1921.
Jackson, E.: Denver M. Times, **20**: 507–510, 1900–1901; Am. J. Ophth. **3**: 150, 1920.
Jaksch, R.: Amtsarzt, **2**: 27–29, 1910.
Jansen, J.: Acta path. et microbiol. Scandinav. pp. 146–153, supp. 26, 1936.
Jelliffe, S. E.: Med. News, **76**: 387–390, 1905.
Jendralski, F.: Deutsche med. Wchnschr. **43**: 1207–09, 1922.
Jephcott, C. M.: Analyst, **60**: 588–592, 1935.
Joffroy and Serveaux: Arch. méd. expér. **8**: 473–90, 1895.
Joiris, N. P.: Arch. Ophth. **52**: 578–581, 1935.
Joyes, C.: Texas State J. M. **10**: 189, 1914–15.
Judd, H. W.: Rep. Surg. Gen. Navy, 195, 1904–5.

Kahlden, V.: Ziegler's Beitr. **9**: 350.

Kazas: Zentralbl. f. Biochem. u. Biophys. **15**: 205, 1919; Vrach. Gaz., S.-Peterb. **16**: 162–164, 1919.

Kazas, I. I.: Novoye v Med. S.-Peterb. **2**: 355–364, 1908.

Keferstein: Ztschr. f. Med.-Beamte, **25**: 221–226, 1912.

Keiser, E.: Arch. f. exper. Path. u. Pharmakol. **14**: 119–285, 1931; ibid. **160**: 687–691, 1931; Deutsche med. Wchnschr. **57**: 398–399, 1931.

Kepter: Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel, **24**: 750–737, 1912.

Klauer, H.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **30**: 280–291, 1939.

Kling, A. & Lassieur, A.: Compt. rend. Acad. d. sc. **73**: 1006–9, 1924.

Knack: Deutsche med. Wchnschr. **45**: 1373, 1919.

Knapp, H.: Arch. Ophth. **20**: 123–130, 1891.

Knies: "The eye in general disease," page 347.

Kobert: "Lehrbuch der Intoxikationen," p. 600; ibid. **24**: 302.

Koelsch: Zentralbl. f. Gewerbehyg. **9**: 198.

Koller, C.: J.A.M.A. **54**: 1866, 1910; Med. Rec. **68**: 10–12, 1905; Mt. Sinai Hosp. Rep. **4**: 376–382, 1905.

Kollo, C., & Crison, N.: Compt. rend. Soc. de biol. **109**: 795–796, 1932.

Kollock, C. W.: J. South Car. M. Ass. **9**: 273–275, 1913.

Komoto, S.: Nippon Gankwa Gakukwai Zasshi, **7**: 318–328, 1904.

Kos, M.: Wien. med. Wchnschr. **4**: 527, 1905.

Kroeber: J. de Pharm. et Chim. **8**: 371, 1913; Pharm. J. **91**: 532, 1914.

Krol, J.: Arch. f. exper. Path. u. Pharmakol. **72**: 444–446, 1913.

Kuhn: Ztschr. f. Med.-Beamte, **25**: 271–21, 1912.

Lamb: Discussion: Moulton, H.: Tr. Oph. Sect. A.M.A. 352–356, 1923.

Lange, W., & Reif, G.: Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel, **41**: 216–226, 1921.

Langgard, A.: Berl. klin. Wchnschr. **49**: 1704, 1912; ibid. **49**: 1704, 1913.

Larkin, J. H., and Jelliffe, S. E.: Med. Rec., **56**: 37–46, 1899.

Leahy, S. R.: New York M. J. **107**: 743, 1918.

Leo, H.: Deutsche med. Wchnschr. **51**: 1062, 1925; abs. J.A.M.A. **86**: 640; Biochem. Ztschr. **191**: 423–38, 1927.

Leschke: Clinical Toxicology, p. 157.

Lesieur, C.: J. de physiol. et de path. gén. 1906, **8**: 427–441.

Leuchke, E.: München. med. Wchnschr. **79**: 714–715, 1932.

Leventhal: Vestnik Oftalmol. **34**: 274–277, 1907.

Levy, Magnus & Stadelmann: Berl. klin. Wchnschr. **49**: 193–198, 1912.

Lewin & Guillery: Handbuch für die gesamte ärztliche Praxis. Berlin: A. Hirschwald, **1**: 372; **2**: 788, 1905.

Lewin, L.: Rev. scient., Par. **1**: 33–40, 1911; Med. klin. **8**: 95–98, 1912; Chem. Zentralbl., 672, 1911.

Lewis, W. K., & Frolich, T. K.: Indust. & Engin. Chem. **20**: 285, 1928.

Lewy, E.: Med.-Chir. Rundschau, p. 508, 1891.

Lightfoot, C. L.: Rep. Proc. Northumb. & Durham M. Soc., Newcastle-upon-Tyne, 71–77, 1890–91.

Loewy and Heide: Biochem. Ztschr. **65**: 230–52, 1914.

Loewy and Muxner: Biochem. Ztschr. **134**: 442–446, 1922–23.

Lormand, Charles: Indust. & Engin. Chem. **17**: 430, 1925.

Lundsgaard, C.: J. Biol. Chem. **33**: 133, 1918; J. Exper. Med. **30**: 271, 1919.

Lyons, A. B.: J. Am. Pharm. A. **11**: 12–15, 682–686, 1922; ibid. **12**: 323–327, 1923.

McConachie, A. D.: Am. Med. **3**: 96, 1902.

McCord, Carey, & Cox, N.: Indust. & Engin. Chem. **23**: 931–36, 1931.

McCoy and Michael: Med. Rec. May 28, 1898.

McIntyre, A. R.: Proc. Soc. Exper. Biol. & Med. **28**: 759–760, 1931.

McKechnie: Canad. M. A. J. **8**: 193.

McLaren, W. M.: Med. World, **19**: 501–503, 1901.

MacFarlan: Pharm. J. **15**: 310–15, 1855–56.

Macht, David I. & Leach, H.: Proc. Soc. Exper. Biol. & Med. **26**: 330–331, 1929.
MacKenzie, G. W.: J. Ophth., Otol. & Laryngol. **26**: 306–308, 1921.
Maiden: Am. J. Ophth. **5**: 653, 1922.
Main: Illinois M. J. **6**: 273, 1904.
Main: Quart. J. Inebr. **25**: 146, 1904.
Mann: Arch. f. wissensch. Mikr., 479, 1894.
Mannich, C.: Arch. d. Pharm. **255**: 261–276, 1917.
Manzoff, C. D.: Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel, **27**: 469, 1914.
Marinesco, G.: Bull. Acad. de méd. **102**: 111–119, 1929.
Marinesco, G., Draganesco, S. Z., & Grigoresco, D.: Semaine med. **2**: 745–748, 1929.
Mashbitz, L. M., Skilianskaya, R. M., & Urevia: J. Indust. Hyg. & Toxicol. **18**: 117–122, 1936.
Masius et Mahaim: Bull. Acad. roy. de méd. de Belg. **26**: 111, 1898.
Matakvin: Protok. zasied. Obsh. Morsk. vrach. v. Kronstadtle, **2**: 5–17 1902–3.
Mathewson, G. H., & Alexander, B.: Canad. M. A. J. **26**: 679–681, 1932.
Matts, M. H.: J.A.M.A. **96**: 460, 1931.
Maue, G.: Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel, **35**: 179–83, 1918.
Mayer: Arch. f. exper. Path. u. Phar. **21**: 122.
Mayer, J. L.: J. Am. Pharm. A. **9**: 508–510, 1920.
Mayer, W.: J. f. Psychol. u. Neurol. **21**: 221, 1915.
Mees, R.: München. med. Wchnschr. **60**: 1200, 1913.
Meller, B.: Arch. f. Psychiat. **76**: 302.
Mendel: Centralbl. f. prakt. Augenh. **43**, 1912.
Mengin: Rec. d'opht., p. 663, 1879.
Mezzatesta, F.: Riv. oto-neuro-oftal. **4**: 258–280, 1927.
Mikhaeloff, S. Ye: Voyenno-Med. J., Petrogr. **243**: 221–250, 1915.
Miller: J.A.M.A. **37**: 1450, 1901.
Miura, S.: Biochem. Ztschr. **49**: 137–143, 144–151, 1913.
Mogelnelskie, B.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **9**: 302, 1927.
Mongel, E. B.: Am. J. Ophth. **3**: 763–765, 1920.
Montgomery, R. J.: Brit. M. J. **1**: 375, 1907.
Morrison, F. A.: Am. J. Ophth. **5**: 645, 1922.
Morson: J. Soc. Chem. Indust. **37**: 26, 1918.
Moulton, H.: Ophth. Rec. **8**: 335–337, 1899; J.A.M.A. **37**: 1447–1451, 1901; Tr. Ophth. Sec., A. M. A., pp. 352–356, 1901.
Moulton, H., & Moulton, E. C.: J. Arkansas M. Soc. **20**: 113, 115, 1923.
Mueller, A.: Zentralbl. f. Gynäk. **44**: 161–170, 1902.
Mueller, B.: Arch. f. Psychiat. **76**: 302–318, 1925.
Muller: Ztschr. f. ang. Chemie, **23**: 351–355, 1910.
Munch & Schwartse: J. Lab. & Clin. M. **10**: 985–996, 1925.
Nagal, C. S.: J.A.M.A. **45**: 1560, 1905.
Natanson, A.: Deutsche med. Wchnschr. **35**: 1871, 1919.
Neiding, Goldenburg, M. N., & Blank, L.: J. Nevropat. i. Psikhist. **24**(2): 67–74, 1931.
Neuberg & M. Kobel: Biochem. Ztschr. **206**: 240–244, 1929.
Neymark, M.: Skandin. Arch. f. Physiol. **73**: 227–236, 1936.
Nicloux, M.: Compt. rend. Soc. de biol. **73**: 59, 1914; J. Physiol. **14**: 916, 1912.
Nicloux, M.: Bull. Soc. chim. biol. **17**: 194–202, 1935.
Nicloux, M., & Placet, A.: Compt. rend. Soc. de biol. **73**: 79, 177–180, 1912; J. de physiol. et de path. gén. **14**: 916, 1912; Compt. rend. Soc. de biol. **73**: 63–66, 1913.
Noe, M.: Biochim. e terap. sper. **16**: 355–366, 1929.
Norris, Chas.: New York M. J. **3**: 583, 1920.

Noviello, L.: Folia med. **21**: 963–975, 1935.
Nuel: Arch. d'opht. **16(8)**: 479, 1900; XIII. Internat. Congress, Paris, 4, 1900.
Odell, H. E.: U. S. Navy M. Bull. **1**: 99, 1907.
Ohlemann: Ztschr. f. Med.-Beamte, **16**: 855–862, 1903.
Olivari: Chem. Zentralbl. **1**: 1780, 1913; Arch. di farmacol. sper. **15**: 83–96, 1913.
Osburne, E. A.: J. M. A. Georgia, **12**: 56–60, 1924.
Pander, H.: Deutsche med. Wchnschr. **53**: 756, 1927.
Pantalioni, M.: Ann. d'ig. **37**: 537, 1927.
Patillo and Colborn: Ophth. Rec. **8(12)**: 599, 1899.
Pearce, A. H.: Boston M. & S. J. **160**: 237–239, 1909.
Phillips: Ophth. Rec., p. 538, 1906.
Picaud: Compt. rend. Acad. d. sc. **124**: 829–831, 1897.
Pincus, F.: Klin. Monatsbl. f. Augenh. 695, 1920; ibid. **65**: 109 abst.
Pohl, J.: Arch. f. exper. Path. u. Pharmakol. **83**: 204–220, 1918.
Poincare: Compt. rend. Acad. des sc. **87**: 682, 1879; **87**: 682, 1878.
Puckner: Western Druggist, December, 1897.
Quittner, S. S.: Cleveland M. J. **13**: 811, 1914.
Rabinovitch, I. M.: Arch. Int. Med. **29**: 821–827, 1922.
Rabuteau, M.: Compt. rend. **81**: 631, 1875.
Raub, J. F.: Ophth. Rec. **8**: 619, 1899.
Ray, J. M.: "Pathology of Eye," 1932 (Friedenwald).
Reif, G.: Arb. a. d. k. Gsndhtsamte. **1**: 50–56, 1915.
Rewiger, K.: Ztschr. f. d. ges. exper. Med. **28**: 368–377, 1922.
Richard, F.: J. de pharm. et chim. **27**: 456–458, 1923.
Ridway, J.: M. Times, **55**: 137.
Rightor, H. H.: J. Arkansas M. Soc. **16**: 49, 1919.
Roberts, T. F.: Texas State J. M. **13**: 391, 1918.
Robinson, J. M.: J.A.M.A. **70**: 148, 1918.
Ronne, H.: Arch. f. Ophth. **77**: 1–95, 1910.
Roosa, D. B. St. J.: Post-Graduate, N. Y. **19**: 855–857, 1904.
Rost: Med. Klin. **8**: 129, 1912.
Rostedt, R.: Finska läk. handl. **63**: 113–26, 1921; abst. J.A.M.A. **77**: 164, 1921.
Ruhle, A.: München. med. Wchnschr. **59**: 964, 1912; Fortschr. d. med. **30**: 1025–1030, 1912; Berl. klin. Wchnschr. **49**: 2128, 1912. Chem. Abst. **6**: 1781, 1912.
Runge, W.: Deutsche med. Wchnschr. **1**: 298–300, 1924.
Sabalitschka: Ber. de Deutsche pharm. Gesellsch. **29**: 214–219, 1919.
Sabbatani: Arch. de fiziol. **7**: 49–80, 1910.
Sadtler: Am. J. Pharm. **77**: 106–110, 1905.
Salm, M.: Texas M. & S. Rec. **1**: 305–309, 1881.
Samelsohn: Arch. f. Ophth. **28**: 1, 1882.
Sammartino, U.: Arch. di farmacol. sper. **56**: 311–319; ibid. 320–326; ibid. 364–371; ibid. 351–363, 1933.
Schaffer, C.: U. S. Navy M. Bull. **6**: 392–394, 1912.
Schenk, P.: Deutsche med. Ztg. **33**: 81, 1912.
Scherwinsky, B.: Arch. f. Ophth. **87**: 135–153, 1914.
Schevitz, J.: Mod. Med., Chicago, **2**: 243, 1920.
Schieck, R.: Ztschr. f. Augenh. **48**: 187, 1922.
Schlossenberger: Quart. J. Chem. Soc. Lond. **3**: 179, 180, 181.
Schmidt, A.: Ztschr. f. Untersuch. d. Lebensmitt. **57**: 584–587, 1929.
Schmiedeberg, O.: Therap. Monatsh. **26**: 329–331, 1912.
Schmiergeld, A., & Guichard, V.: Encéphale, **2**: 602–605, 1908.
Schultze, Otto: J.A.M.A. **70**: 144, 1918.
Schweissinger: München. med. Wchnschr. **26**: 329–331, 1912.
Schyver, S. B., & Wood, C. C.: Analyst, London, **45**: 164–170, 1920; Am. J. Pharm. **92**: 720–728, 1920.

Scott, R. W., & Hanxlik, P. J.: J.A.M.A. **74**: 1000, 1920.
Scudder: J. Am. Chem. Soc. **27**: 892, 906, 1905.
Segale: Zentralbl. biochem. Biophys. **14**: 446, 1912; Berl. klin. Wchnschr. **50**: 255–256, 1913.
Semichan, L., & Flanzy, M.: Ann. d. falsif. et d. fraudes, **24**: 80–87, 1931.
Shannon: Arch. f. Ophth. **7**: 813, 1932.
Sherer, J. W.: Tr. Mississippi Valley M. Ass., 1902.
Siegrist, A.: Arch. f. Augenh. **41**: 65–67, 1900.
Sklianskaya, Urieva, & Mashbitz: J. Indust. Hyg. & Toxicol. **18**: 106–116, 1936.
Smirnoff, Ya. A.: Vestnik oftal. M. **26**: 439, 1909.
Sollmann: J. Pharm. & Exper. Therap. **16**: 291–309, 1920. "Pharmacology," 1932.
Soupault et Achard: Arch. de méd. expér. et d'anat. path. **5**: 359, 1893.
Sprague: Dominion M. Monthly, **24**: 11–16, 1905.
Stadelmann: Ztschr. f. arztl. Fortbild. **9**: 481, 523, 1912.
Stadelmann & Magnus-Levy: Berl. klin. Wchnschr. **49**: 193, 1912.
Stadie, W. C.: J. Exper. M. **33**: 627, May, 1921; J. Biol. Chem. **41**: 237, 1920.
Stapel, F.: Monatschr. f. Psychiat. u. Neurol. **29**: 216–236, 1911.
Steiger, O.: München. med. Wchnschr. **65**: 753–755, 1918.
Steindorff: Deutsche med. Wchnschr. **47**: 246, 1921.
Stillson, J. O.: Tr. Indiana M. Soc. 44–46, 1898.
Stirling, J. W.: Ophth. Rec. **24**: 38–40, 1905.
Strader, G. L.: Am. J. Ophth. **10**: 359, 1927.
Strassman: New York M. J. **140**: 583–585, 1920.
Straus et Blocq: Arch. de phys. p. 408, 1887.
Stricker: Lancet-Clinic, **99**(16): 481, 1908.
Strohmberg, C.: St. Petersb. med. Wchnschr. **29**: 421, 1904; ibid. **31**: 55–57, 1906.
Suker: Am. J. Ophth. **3**: 534, 1920.
Super: Am. J. Ophth. **5**: 377, 1922.
Swadener, E. L.: J.A.M.A. **60**: 1479, 1913.
Takahashi, T., Gunke, M., & Yamaxaki, T.: J. Am. Chem. Soc. **29**: 2723–2726, 1917.
Tankersley, Grace: J.A.M.A. **98**: 2011, 1932.
Taylor: N. Y. Med. J. **1812**: 580, 1920.
Taylor, A. E.: J. Biol. Chem. **15**: 217–220, 1913–14.
Tendler, G., & Mannich, C.: Arb. a. d. pharmazeut. Inst. d. Univ. Berl. **3**: 243–260, 1906.
Thompson, A. G.: Ophth. Rec. **6**: 579–582, 1897.
Thoms, H.: Arb. a. d. pharmazeut. Inst. d. Univ. Berl. **9**: 202–204, 1912.
Trumper, M.: Internat. Clin. **1**: 84–88, 1931.
Turche, L.: Arch. f. phys.-diätet. Therap. **14**: 164–168, 1912.
Tyrer and Gosling: Yearbook of Pharm., 434, 1912.
Tyson, H. H.: Arch. Ophth.; Zentralbl. Biochem. & Biophys. **15**: 205, 1912; Arch. Ophth. **41**: 459–471, 1912; Med. Times, **44**: 40, 1916.
Tyson & Schoenberg: J.A.M.A. **63**: 915, 1914; Sec. of Ophth., A.M.A., 1914; Arch. Ophth., 275–280, 1915; Chem. Absts. **9**: 2942, 1915.
Uhthoff, W.: Arch. f. Ophth., 257, 1887; XIII. Internat. Congress, Paris, 1900; Klin. Monatsbl. f. Augenh. **19**: 48–55, 1915.
Ustvedt, H. J.: Acta med. Scandinav. pp. 857–858, Supp. 78, 1936; Acta path. et microbiol. Scandinav. pp. 145–146, Supp. 26, 1936.
Vandevelde: Chem. Abstr., 1914, **8**: 3451. Biochem. Ztschr. **63**: 402–408, 1914.
Van Fleet, F.: Manhattan Eye & Ear Hosp. Rep. **4**: 15, 1897; Med. Rec. **61**: 91–93, 1902; Quart. J. Inebr. **24**: 459–467, 1902.
Van Slyke, D. D.: J. Biol. Chem. **41**: 567, 1920; ibid. **33**: 127, 1918.
Vas: Arch. f. exper. Path. 141, 1894.

Vayntsvayg, O. M., Kleybs, B. D., & Pasternak, A. E.: Sovet. vestnik oftal. **3**: 157–167, 1933.
Viger: Rec. d'ophtal., p. 636, 1877.
Vivario, R.: J. de pharm. et de chir. **10**: 145–147, 1914.
Voegtlin, Carl: Congressional Record, June 5, 1930.
Voltz, W.: Med. Klin. **8**: 697, 1912.
Von Buchla, K.: Klin. therap. Wchnschr. **19**: 673–680, 1912.
Von Fellenberg: Ztschr. f. Untersuch. d. Lebensmitt. **74**: 485–487, 1937; Mitt. a. d. Geb. d. Lebensmitt. u. Hyg. **5**: 225–226, 259–261, 1914.
Von Romburg: Schimmel's Ber., 1894, 1896, 1897, 1898.
Vossius: Arch. f. Ophth. **28**(**3**): 201.
Wasserman & Keysser: Ztschr. f. Hyg. u. Infektionsk. **68**: 535–550, 1911; also, folia serolog. **7**: 243–251, 1911.
Webster, D.: Med. Rec. **18**: 649–655, 1880.
Weese, H.: Arch. f. exper. Path. u. Pharm. **135**: 118–130, 1928.
Weil, A.: "Textbook of Neuropathology," p. 191, 1933.
Welmer: Tr. Am. Ophth. Soc. **12**: 523, 1911.
Wersen, A.: Svenska läk-tidning, **17**: 1025–1032, 1920.
Wheelock, K. K.: J.A.M.A. **12**: 292–295, 1889.
Whitney: Am. J. Physiol. **30**: 463, 1912.
Widmark & Bildsten: Biochem. Ztschr. **148**: 325–335, 1924.
Wilder, W. H.: Ophth. Sec., A.M.A. **13**: 197, 1904.
Wiley: New York M. J. **80**: 1098, 1904; ibid. **71**: 97, 1905.
Willcox, W.: Brit. J. Inebr. **27**: 64–71, 1929.
Willemse, A.: Nederl. tijdschr. v. geneesk. **80**: 5118–5120, 1936.
Williams, J. F.: Indust. & Engin. Chem. **19**: 844.
Wilmer: Tr. Am. Ophth. Soc. **12**: 523, 1911.
Windall: Allm. svenska läk-tidning, **2**: 289–293, 1905.
Wirthle, F.: Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel, **23**: 14–29, 345, 1912.
Wood: J.A.M.A. **43**: 972, 1058, 1117, 1213, 1904; ibid. **59**: 1962–6, 1912; New York M. J. **81**: 5, 1905.
Wood, C. A.: Brit. M. J. **2**: 1855–1858, 1906; J.A.M.A., p. 1220, 1904; New York M. J. **81**: 5–11, 1905; Internat. Clin. **1**: 68–78, 1906; J.A.M.A., p. 1962, 1912.
Wood, C. A., & Buller, F.: J.A.M.A. **43**: 972–977, 1058, 1062, 1117, 1123, 1213, 1221, 1289, 1296, 1904.
Woodruff, J. C.: Indust. & Engin. Chem. **19**: 1147, 1927.
Woods, H.: J.A.M.A. **9**: 1762–1764, 1913.
Würdemann, H. V.: Am. Med. **2**: 995–997, 1901.
Yakovleva, A. A.: J.A.M.A. p. 1316, 1915.
Yant & Frey: Indust. & Engin. Chem. **17**: 692, 1925.
Yant, Schrenk, & Sayers: Indust. & Engin. Chem. **23**: 551–555, 1931.
Yant, W. P., & Schrenk, H. H.: J. Indust. Hyg. & Toxicol. **19**: 337–345, 1937.
Yasaka, A., & Akimoto: Nippon Gankwa Gakukwai Zasshi, Tokyo, **6**: 651–704, 1902.
Yoshida, M.: J. Exper. Med. **23**: 434–438, 1934.
Yttri, J.: Tidsskr. f. d. norske Lægefor. Kristiania, **39**: 315, 1919.
Zenon Pupier: Arch. d. physiol., p. 417, 1888.
Zethelius, M.: Hygiea, Stockholm, **82**: 45, 1920.
Zethelius & Wersen: Klin. Monatsbl. f. Augenh. **65**: 51, 1920; abst. Ophth. Lit. Sept., 1921.
Ziegler: J. of Adv. Therap. May, 1907.
Ziegler, Lewis: Arch. Ophth. p. 516, 1914.
Ziegler, S. L.: Ophthalmology, **7**: 599–607, 1910–11; Brit. J. Ophth. **5**: 365, 1921; N. York State J. M. **21**: 288, 1921.
Zienkiewicz, A.: Polska gaz. lek. **11**: 471–472, 1932.